

Appendices

Appendix A: Search Strategies

Main Search, MEDLINE (1966 to August Week 3 2008)

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 2008 Week 36)

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, 2008)

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 3 2008)

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. Clofibrac acid/
 82. Clofibrate/
 83. Bezafibrate/
 84. Gemfibrozil/
 85. Procetofen/

86. (gemfibrozil or fenofibrate or bezafibrate or clofibrate or clofibrac 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 2008 Week 36)

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 gastrototoxic\$).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 August Week 3 2008)

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

Appendix B: Excluded Studies

Excluded Studies - FullText Relevance

Do Not Directly Address the Key Questions

Aberg JA, Zackin RA, Brobst SW, 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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Appendix C: Drugs Included in the Review and Label Information

Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
HMG-CoA reductase inhibitors (Statins) inhibit conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, an early step in the cholesterol biosynthetic pathway Contraindications: active liver disease; unexplained persistent ↑ transaminases; pregnancy; lactation Withhold therapy if patient is experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.					
Atorvastatin Calcium	Lipitor®	Plasma peak: 1-2 h Bioavailability: 14% systemic; 30% Absorption ↓ with food but LDL-c reduction similar regardless of food Highly plasma protein- bound ½-life: Plasma ~14h; Activity 20-30 h Fecal excretion In liver ↓ LDL receptors on the cell-surface ↑ cellular uptake and catabolism of LDL Metabolized by CYP450 3A4	↓ TC, LDL-c, Apo B, and TG levels and ↑ HDL-c in FH, nFH, and mixed dyslipidemia (Types IIa and IIb) ↓ serum TG levels (Type IV) Primary dysbetalipoproteinemia (Type III) ↓ total-C, LDL-C in HoFH‡ ↓ risks of myocardial infarction, stroke, angina, need for revascularization, and hospitalization for congestive heart failure, in CHD Contraindications: ↑ CPK	10, 20, 40, 80 mg tablets Initially 10 mg/d; max 80 mg/d Titrate q 2-4 wks as appropriate May be combined with bile acid sequestrants; maximize time between agents Do not combine with fibrates Ator levels, myopathy and/or rhabdomyolysis risk ↑ with concurrent cyclosporine, fibrates, niacin, CYP450 3A4 substrates§	↑ Cmax, ↑ AUC in people > 65y compared to younger adults ↑ Cmax, ↓AUC in women compared to men (no significant difference in LDL↓) ↑ AUC of concomitant norethindrone and ethinyl estradiol contraceptives

Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Fluvastatin sodium or Fluvastatin sodium Extended-Release	Lescol® or Lescol® XL	Plasma Peak Lescol < 1h; Lescol XL ~ 3h Absorption slower but not decreased with food ↑ Cmax, AUC with hepatic insufficiency Highly variable pharmacokinetics [with doses > 20mg, enantiomer differences at peak] Highly plasma protein-bound Metabolism by CYP450 2C9 (75%), 2C8 (~5%), 3A4 (~20%) Excretion: 90% feces; primarily metabolites	↓ TC, LDL-c, Apo B, and TG levels and ↑ HDL-c in HeFH, nFH, and mixed dyslipidemia (Types IIa and IIb) ↓ need for revascularization procedures, slow coronary atherosclerosis in CHD	20, 40 mg Lescol® capsules and 80 mg Lescol® XL tablets Initial dose 20 mg, titrate q 6-wks as indicated by lipid levels and liver function For LDL-c ↓ >25%, or initial LDL-c >190mg/dL, consider initial dose of 40-80 mg/d Adolescents >1y post-menarche with HeFH, LDL-c >190 mg/dL, family history of CVD and 2+ risk factors Interactions: ↑ Fluv Cmax, AUC with cyclosporine ↓ Fluv Cmax, AUC, ↑ plasma clearance with Rifampicin ↑ Fluv Cmax, AUC, ↓ plasma clearance with Cimetidine, Ranitidine, Omeprazole ↑ phenytoin and Fluv Cmax and AUC when used concomitantly ↑ Diclofenac Cmax, AUC with Fluv ↑ Glibenclamide (Glyburide) Cmax, AUC, t½, with Fluv – monitor carefully	Renal insufficiency – no adjustment necessary Hepatic insufficiency – caution with history of liver disease or heavy alcohol ingestion Monitor prothrombin times with warfarin
Lovastatin	ALTOCOR™ Extended release	Inactive lactone metabolized to beta-hydroxyacid and further active metabolites Absorption: ~ 30% Excretion: primarily feces; ~10% urine Crosses placenta and blood-brain barrier Highly plasma protein-bound CYP450 3A4 substrates§ ↑ drug exposure, myopathy risks	↓ LDL-C, Total-C, TG; ↑ HDL-C in HeFH, nFH, mixed dyslipidemia (Type IIa, IIb) Less effective, more incidents of ↑ transaminases in HoFH	10, 20, 40, 60 mg tablets 1 tab at bedtime; start low, titrate q 4 wks ≤ 20 mg if taken with niacin ↑ myopathy with fibrates, >1g/day niacin, cyclosporine, CYP450 3A4 substrates§	↓ LDL-C, Total-C, variable ↓ TG, variable ↑ HDL-C drug exposure ↓ with food

Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Pravastatin sodium	PRAVACHOL®	Drug in active form Elimination ½ life 77 h Highly variable plasma peak and AUC for healthy and cirrhotic subjects Evening dose ↓ systemic bioavailability; ↑ efficacy ~20% plasma protein-bound ~50:50 renal:fecal excretion Not metabolized by CYP450 3A4	↓ risk of MI, need for revascularization, death from cardiac events, with HC, with and without clinically evident CHD ↓ risk of stroke, slow coronary atherosclerosis in CHD ↓ LDL-C, Total-C, Apo-B, VLDL-c, TG; ↑ HDL-C in HeFH, nFH, mixed dyslipidemia (Type IIa, IIb) ↓ TG (Type IV) Primary dysbetalipoproteinemia (Type III) [labelled for children >8]	10, 20, 40, 80 mg tablets Initial 40 mg/d od; max 80 mg/d Administer 1h before or 4h after bile acid sequestrant No ↑ risk myopathy with concurrent therapy with niacin, fibrates, CYP450 3A4 substrates§	Renal insufficiency 10 mg/d
Rosuvastatin calcium	CRESTOR®	Peak plasma concentration 3-5h; Primarily plasma protein-bound Bioavailability: ~20% Elimination half-life: ~19hrs Excretion: 90% in feces Unknown transfer to milk ~ 2X exposure in Asian patients compared to Caucasian Metabolized “minimally” by CYP 450-2C9; no effect on CYP 450 3A4	↓ Total-c, LDL-c, ApoB, non-HDL-c, TG, and ↑ HDL-C in Primary hypercholesterolemia (HeFH and nonfamilial) and mixed dyslipidemia (Types IIa and IIb) ↓ TG (Type IV) HoFH ± Not studied in Type I, III and V Slow progression of atherosclerosis in adults	5, 10, 20, 40 mg tablets Initial dose 10 mg/d except as noted. ≤ 5 mg/d with cyclosporin ≤ 10 mg/d with Lopinavir/Ritonavir ≤ 10 mg/d in combination with gemfibrozil Use Mg or Al containing antacids 2h before or after Rosuvastatin ↑ risk myopathy and/or rhabdomyolysis, acute renal failure with higher dose, concurrent lipid lowering therapy, cyclosporine, lopinavir/ritonavir	HoFH and/or LDL-c >190 mg/d: 20-40 mg/d Asian: 5 mg/d initially Elderly: use with caution Severe renal impairment not on dialysis: 5-10 mg/d (~ 3X ↑ plasma concentration) Prolongs INR with coumarin anti-coagulant - monitor INR frequently Use with caution with drugs that reduce endogenous steroid hormones (e.g. ketoconazole, spironolactone, and cimetidine) ↓ dose with warfarin

Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications [†] (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Simvastatin	ZOCOR [®]	Plasma peak: ~ 2-4h Plasma half-life: 4-12 h Lactone hydrolyzed to β-hydroxyacid Low bio-availability in the circulation (<5%) ↑ levels with age, and renal and hepatic insufficiency Extensive first-pass extraction in the liver Highly plasma protein-bound Excretion: ~ 60% feces; ~ 13% urine No CYP450 3AC inhibition CYP450 3AC substrate	↓ risk of MI, need for revascularization, death from cardiac events, risk of stroke, TIA in HC patients with clinically evident CHD; ↓ TC, LDL-c, Apo B, non-HDL-c-c, TG; ↑ HDL-c in primary Hypercholesterolemia (HeFH and nonfamilial) Mixed dyslipidemia (Types IIa and IIb) Dysbetalipoproteinemia (Type III) Hypertriglyceridemia (Type IV hyperlipidemia) HoFH [‡] Also labeled for pediatric uses	5, 10, 20, 40, 80 mg tablets 20 mg/d od in evening; titrated monthly as indicated clinically HoFH: 40 mg/d in evening or 80 mg/d in 3 divided doses ↑ myopathy with fibrates, >1g/day niacin, cyclosporin, CYP450 3A4 substrates [§] , HIV protease inhibitors	With concomitant lipid lowering therapy: ≤ 10 mg/d With cyclosporine or Danzol: initially 5 mg/d; ≤ 10 mg/d maximum With Amiodarone or Verapamil: ≤ 20 mg/d Renal insufficiency: 15 mg/d initially with close monitoring Contraindications: hypersensitivity, active liver disease; unexplained persistent ↑ transaminases; pregnancy; lactation

Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Ezetimibe selective inhibitor of intestinal cholesterol and related phytosterol absorption by the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), in the brush border of the small intestine					
Ezetimibe	Zetia®	Plasma peak: 4-12 h Plasma half-life: ~ 22 hrs Highly plasma protein-bound Absorption: High inter-subject variability; unaffected by food Glucuronide conjugation ↑ levels in geriatric patients Excretion: ~ 80% feces Neither inhibitor nor inducer of CYP450 isozymes 50-80% ↓ AUC with cholestyramine bid	↓ Total-c, LDL-c, ApoB in primary hypercholesterolemia (HeFH and nonfamilial) - monotherapy and in combination with HMG-CoA inhibitors ↓ Total-c, LDL-c, ApoB, non-HDL-c-c in mixed hyperlipidemia - combination therapy with FF HoFH: in combination with Ator or Sim * ↓ sitosterol and campesterol in HoFS As appropriate upon hospitalization for an acute coronary event	10 mg tablets 10 mg od May be administered with HMG-CoA reductase inhibitor or fibrate, with awareness that monotherapy risks of other medications are magnified with co-therapy	Hepatic insufficiency: no adjustments required Renal insufficiency: no adjustments required ≥ 2 h before or ≥ 4 h after bile acid sequestrant None for race Contraindications: hypersensitivity, active liver disease; unexplained persistent ↑ transaminases; pregnancy; lactation Rhabdomyolysis and myopathy are rare on monotherapy; generally associated with concomitant use of HMG-CoA reductase inhibitor

Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications [†] (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Ezetimibe/ Simvastatin	Vytorin™	Same as individual drugs above 55% ↓ AUC with bile acid sequestrant	↓ Total-c, LDL-c, ApoB, non- HDL-c, TG, and ↑ HDL-C in primary HC or mixed hyperlipidemia. (HeFH and nonfamilial) ↓ Total-c, LDL-c in primary or mixed hypercholesterolemia HoFH *	10/10, 10/20, 10/40, 10/80 mg ezetimibe/mg Sim od evening, with or without food Primary HC initially 10/10 or 10/20, titrated monthly as clinically appropriate HoFH: 10/40 - 10/80 mg/d 10/10 max with gemfibrate; caution with other fibrates, ≥1 g/d niacin With bile sequestrants, dose ≥2 h before or ≥4 h after sequestrant risk of myopathy and/or rhabdomyelitis ↑ with dose, CYP450 3A4 substrates [§] 55% ↓ AUC with cholestyramine – not recommended Monitor with concomitant digoxin, warfarin	Hepatic insufficiency: not recommended Renal insufficiency: use only if Sim ≥5 mg is tolerated. ≤10/10 mg/d with cyclosporine or Danazol only if Sim ≥5 mg tolerated ≤ 10/20 mg/d with Amiodarone or Verapamil Other concomitant lipid lowering therapy: avoid - lack of safety and effectiveness data. If used, dose ≤ 10/10 mg/d Contraindications: hypersensitivity, active liver disease; unexplained persistent ↑ transaminases; pregnancy; lactation

Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Fibrates					
Fenofibrate	TRICOR®	Insoluble in water, but readily absorbed from GI tract; ↑ absorption with food Plasma Peak fenofibric acid 6-8h Elimination t _{1/2} 20h Steady-state after 5 days dosing Highly plasma protein-bound Glucuronide conjugation Elimination: 60% of a dose in urine; 25% feces Insignificant oxidative metabolism (e.g. CYP450) Finobrate and fenofibric acid do not inhibit CYP450 3A4, 2D6, 2E1, 1A2; are weak inhibitors of 2C19, 2A6; mild-to-moderate inhibitors of 2C9	↓ Total-c, LDL-c, TG, ApoB; ↑ HDL-c in primary HC (HeFH and nFH; Types IIa and IIb) - monotherapy and with statins ↓ TG in Types IV and V hyperlipidemia Contraindications: hypersensitivity; severe renal or hepatic dysfunction; unexplained persistent liver function abnormality; preexisting gallbladder disease	54, 160 mg tablets Initial dose 160 mg/d with normal renal function; reduce dose if lipid targets met Limit dose to 54 in those with moderate renal impairment, and in elderly Coumarin-type anticoagulants potentiated – monitor prothrombin times Immunosuppressants (e.g. cyclosporine) may elicit synergistic nephrotoxicity Bile acid sequestrants 1-2h after or 4-6h before fenofibrate Combine with HMG-CoA reductase inhibitors only if benefit outweighs increased risk including myopathy and/or rhabdomyelitis	
Micronized fenofibrate	Lofibra®	30% ↑ absorption compared to TRICOR®, so lower once-daily dose is effective	As above	134, 200 mg tablets	

Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Gemfibrozil	LOPID®	Completely absorbed ↑ Cmax with dose 0.5h before meal; unchanged AUC ↓ AUC with dose after meal Highly plasma protein- bound 6% excreted in feces 70% excreted in urine; glucuronide conjugation Oxidative metabolism	↓ TG in Types IV and V hyperlipidemia at risk of pancreatitis Not indicated for Type I hyperlipoproteinemia, ↓ risk of developing CHD only in Type IIb patients with low HDL-c, high LDL-c and TG Contraindications: combination with cerivastatin (↑ risk myopathy and/or rhabdomyelitis); hepatic or severe renal dysfunction, including primary biliary cirrhosis; gallbladder disease; hypersensitivity	600 mg tablets 1200 mg/d; 600 bid, 0.5h before morning and evening meals Coumarin-type anticoagulants potentiated – monitor prothrombin times Patients taking repaglinide or gemfibrozil should not start the other; patients taking both already should carefully monitor blood glucose, and should not take itraconazole. Discontinue if lipid response not significant	Caution in pregnancy – only if potential benefit outweighs risks to fetus Unknown transfer to breast milk

Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications [†] (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Niacin					
Niacin (NIR)	Niacor [®]	Water-soluble B-complex vitamin (note: nicotinamide not effective) Plasma peak: 30-60 min Plasma t _{1/2} : 20-45 min Excretion: 88% in urine as niacin and nicotinuric acid	↓ Total-c, LDL-c in primary HC (Types IIa and IIb) ↓ TG in hyperlipidemia (Types IV and V), ↑ HDL-c Not indicated in Type I hyperlipoproteinemia Contraindications: hypersensitivity; significant/unexplained hepatic dysfunction; active peptic ulcer; arterial bleeding	500 mg tablets 1-2 g, bid or tid Start with 250 mg following evening meal, increase every 4-7 days until 2 g/d. If lipid goals are not met, increase at 2-4 wk intervals to 3g/d. May increase further, generally 6g/day max. Flushing may be decreased by slowly increasing dose, pre-treatment with aspirin or other NSAID.	Use with caution: substantial alcohol consumption; history of peptic ulcer; hepatitis; hepatobiliary disease; diabetes or potential diabetes; unstable angina/MI (esp. with nitrate, calcium channel blockers or adrenergic blocking agents); increased risk R/M with HMG-CoA reductase inhibitors Pregnancy: discontinue Tx for Types IIa or IIb; assess individually for Types IV or V Nursing: transfers to milk - assess individually

Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Niacin extended-release (NER)	NIASPAN®	Plasma half-life: NR Absorption: 60 to 76 % of dose Excretion: 60 to 76 % of dose recovered in urine; little in feces Distribution: In mice niacin and metabolites concentrate in the liver, kidney and adipose tissue. Complex metabolism	↓ Total-c, LDL-c, Apo-B and TG in primary hypercholesterolemia (HeFH and nonfamilial) and mixed dyslipidemia (Types IIa and IIb) ↓ TC in Types IV and V hyperlipidemia ↓ risk recurrent MI with history of MI and HC In combination with Lov (see below) In combination with bile acid sequestrant to slow or reverse atherosclerotic disease; ↓ Total-c, LDL-c in primary hypercholesterolemia (Type IIa) Contraindications: hypersensitivity; significant, unexplained hepatic dysfunction; active peptic ulcer; arterial bleeding	500, 750, 1000 mg Tablets swallowed whole, according to a titration schedule, at bedtime, after a low-fat snack Flushing a common side-effect - reduced with aspirin or other NSAID, avoidance of hot drinks. If awakened by flushing rise carefully, esp. if taking blood-pressure medication Retitrate after extended discontinuation Maximize time between bile acid sequestrants and niacin May be added for patients on stable dose Lov, max Lov 20 mg/d, and Niaspan 2 g/d	Caution, monitor closely: hepatic insufficiency; history of jaundice, hepatobiliary disease, peptic ulcer; renal insufficiency; diabetes/potential diabetes – monitor for dose-related ↑ glucose intolerance; unstable angina/MI (esp. with nitrate, calcium channel blockers or adrenergic blocking agents); predisposition to gout May potentiate effects of anticoagulants Monitor for hypophosphatemia Pregnancy: discontinue Tx for Types IIa or IIb; assess individually for Types IV or V

Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications [†] (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Niacin extended-release / lovastatin	Advicor [®]	Plasma peak: Niacin 5h; Lov 2-4h Plasma half-life: Niacin 20 to 48 min; Lov 4.5 h Absorption: Niacin ~72%; systemic concentrations dose-dependent and variable; Lov Bioavailability of Niacin and Lov varies with food; tablets not interchangeable Distribution: Niacin <20% serum protein-bound, distributes into milk; Lov highly serum protein- bound Lov bioavailability ↑ with CYP450 3A4 substrates [§] Excretion: >60% Niacin in urine; ~83% Lov in feces [check to make consistent with 2 ingredients above]	Not for initial therapy Primary hypercholesterolemia (HeFH and nonfamilial) and mixed dyslipidemia (types IIa and IIb) Patients treated with Lov needing lower TG or higher HDL; and Patients treated with niacin who require further LDL- lowering Contraindications – see niacin and Lov	500/20, 750/20, 1000/20 mg niacin/mg Lov Add Lov to existing niacin therapy, or titrate niacin Warning: do not substitute with equivalent dose used of crystalline niacin – possible severe hepatotoxicity Caution: alcohol consumption, history of liver disease Avoid concomitant use of fibrates unless benefit likely to outweigh potential harm (e.g. hepatotoxicity, myopathy and/or rhabdomyelitis) See also Lov, niacin	No dose adjustments reported for special populations.

Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Bile acid sequestrants - Strong acid ion exchange resins that are not bioabsorbed, to remove bile acids from hepatic re-circulation Contraindicated with bowel obstruction or hypersensitivity to agent					
Cholestyramine	Cholestyramine	Hydrophilic In patients with partial biliary obstruction, ↓ dermal deposition lessens pruritis??	↓ LDL-c in HC Not indicated for TG only	9 g/dose (packet or scoop) mixed with liquid 1 dose od; titrated to bid after 1wk; recommended maintenance 2-4, max 6g/d as appropriate May reduce absorption of many medications and nutrients (vitamins, phosphate) – use caution when titrating dose and when discontinuing	Caution re. constipation, possible bowel obstruction; tooth discoloration, damage Caution in pregnancy/nursing due to possible nutrient deficiencies
Colestipol	Cholestid	Not applicable		5 g/scoop granules 1g tablets	
Colesevelam	Welchol	Hydrophylic, insoluble in water, not degraded by digestive enzymes Binds bile acids, including glycholic acid	Alone or with a statin to ↓ LDL-c in primary hypercholesterolemia (Type IIa)	625 mg tablets 6 tablets od or 3 bid with meals, with liquid; max 7/d No ↓ bioavailability of digoxin, Lov, metopropol, quinidine, valproic acid and warfarin Slight ↓ bioavailability verapamil	Caution re. susceptibility to vitamin K or fat-soluble vitamin deficiencies Caution re. dysphagia, swallowing disorders, severe gastrointestinal motility disorders, or major gastrointestinal tract surgery Consult physician if intending conception, pregnant or nursing

Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications [†] (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Omega-3 fatty acids					
Omega-3-acid ethyl esters	OMACOR®	Highly absorbed Mechanism poorly understood Dose-dependent ↑ serum phospholipid EPA; less marked ↑ DHA not dose-dependent Human CYP450 unknown; ↑P450 enzyme concentrations in rats	↓ very high TG (≥ 500 mg/dL) Contraindications: hypersensitivity, allergy or hypersensitivity to fish	1 g capsules (900 mg ethyl esters of omega-3 fatty acids) ~ 465 mg EPA ~ 375 mg DHA Dose: 4 g od or 2 g bid Discontinue after 2 mo if response is inadequate	Pregnancy: not studied – discontinue if pregnant or nursing Anticoagulants: monitor for increased bleeding ALT may increase in isolation - monitor

Abbreviations: ALT = Alanine transaminase, AST = aspartate transaminase, AUC = area under the curve in pharmacokinetic study, Apo A = Apo B, Cmax = maximum plasma concentration, CHD = coronary heart disease, CPK = creatine phosphokinase, d = day, DHA = docosahexaenoic acid, EPA, eicosapentaenoic acid, FH = Familial hypercholesterolemia, GI = gastrointestinal, HC = hypercholesterolemia, HoFH = Homozygous familial hypercholesterolemia, HeFH = Heterozygous familial hypercholesterolemia, HoFS = Homozygous familial sitosterolemia, LDL –c low density lipoprotein cholesterol, max = maximum, MI = myocardial infarction, mo = month, NAR = no adjustments required, nFH = Non-familial hypercholesterolemia, NR = not reported, NSAID = non-steroidal anti-inflammatory drug, od = once daily, t_{1/2} = half-life (time for concentration to decrease to half the initial level), TG = triglycerides, TIA = transient ischemic attack, Tx = treatment

Footnotes:

* Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

[†] Hypersensitivity is a contraindication for all medications.

‡ as an adjunct to or in place of other treatments (e.g., LDL-c apheresis)

§ e.g. itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice.

Appendix D: Planned Analyses

Outcome	Sensitivity analysis	Data	Any statin	Ator	Sim	Ros	Prava	Fluv	Lov
				Lower dose statin in combination versus higher dose monotherapy Fixed dose or fixed titration All dosing schedules, including conditional titration					
All-cause mortality		n/N	A, R, S	A, R, S	A, R, S	A, R, S	R, S	R, S	R, S
All-cause mortality	AAC	n/N	A, R, S	A, R, S	A, R, S	A, R, S	R, S	R, S	R, S
Vascular death		n/N	A, R, S	A, R, S	A, R, S	A, R, S	R, S	R, S	R, S
Vascular death	AAC	n/N	A, R, S	A, R, S	A, R, S	A, R, S	R, S	R, S	R, S
Fatal myocardial infarction		n/N	A	A	A	A			
Nonfatal myocardial infarction		n/N	A	A	A	A			
Any (STEMI and/or non-STEMI) or unspecified myocardial infarction		n/N	A	A	A	A			
Any cerebrovascular event		n/N	A	A	A	A			
Hemorrhagic stroke		n/N	A	A	A	A			
Ischemic stroke		n/N	A	A	A	A			
TIA		n/N	A	A	A	A			
Any or unspecified stroke		n/N	A	A	A	A			
Acute coronary syndrome		n/N	A	A	A	A			
Carotid endarterectomy		n/N	A	A	A	A			
Percutaneous coronary intervention		n/N	A	A	A	A			
CABG		n/N	A	A	A	A			
Revascularization procedures		n/N	A	A	A	A			
For all clinical outcomes, conduct additional analyses on trials of followup duration of 24 weeks or more									
Treatment Adherence		n/N	A	A	A	A			

[illegible]

Outcome	Sensitivity analysis	Data	Any statin	Ator	Sim	Ros	Prava	Fluv	Lov
		Mean % change from baseline OR change score	A, R, S	A, R, S	A, R, S	A, R, S	R, S	R, S	R, S
Non-HDL-c									
		Mean % change from baseline OR change score	S (diabetes mellitus subgroup only)	S (diabetes mellitus subgroup only)	S (diabetes mellitus subgroup only)	S (diabetes mellitus subgroup only)	S (diabetes mellitus subgroup only)	S (diabetes mellitus subgroup only)	S (diabetes mellitus subgroup only)
Triglycerides									
		Mean % change from baseline OR change score	S (diabetes mellitus subgroup only)	S (diabetes mellitus subgroup only)	S (diabetes mellitus subgroup only)	S (diabetes mellitus subgroup only)	S (diabetes mellitus subgroup only)	S (diabetes mellitus subgroup only)	S (diabetes mellitus subgroup only)
Carotid artery									
		IMT (mm)	A	A	A	A			
		plaque area	A	A	A	A			
		plaque volume	A	A	A	A			
		%stenosis	A	A	A	A			
		calcif'n	A	A	A	A			
Coronary artery									
		IMT (mm)	A	A	A	A			
		plaque area	A	A	A	A			
		Plaque volume	A	A	A	A			
		%stenosis	A	A	A	A			
		calcif'n	A	A	A	A			

Abbreviations: A = analyses of all study populations, AAC = adequate allocation concealment; calcif'n = calcification, Any statin = Any statin (including mixed) + nonstatin drug, versus any statin (including mixed) of any dose, Ator = Atorvastatin 5-20 mg/day + nonstatin drug, versus Atorvastatin 40-80 mg/day, CABG = coronary arterial bypass graft, Fluv = Fluvastatin 5-40 mg/day + ezetimibe 10 mg/day, versus Fluvastatin 80 mg/day, IMT = intima-media thickness, Lov = Lovastatin 5-40 mg/day + another hypolipidemic versus Lovastatin 80 mg/day, n = number with particular outcome in statistical analysis, N = total number in group or trial, Prava = Pravastatin 5-40 mg/day + another hypolipidemic drug, versus Pravastatin 80, R = populations requiring intensive lipid-lowering therapy, Ros = Rosuvastatin 5-10 mg/day + nonstatin drug versus Rosuvastatin 20-40 mg/day, S = pre-specified subgroups, Sim = Simvastatin 5-20 mg/day + nonstatin drug, versus Simvastatin 40-80 mg/day, TIA = transient ischemic attack

Appendix E: 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 $\leq 50\%$; 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.

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Abbreviations

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

Table E-1. Within-trial, within-treatment pooling of multiple treatment group data for clinical outcomes

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
All cause mortality			
Durrington (2004)¹²⁵	Rosuvastatin 40	NONE	53
	Rosuvastatin 10	Fenofibrate 67	53
	Rosuvastatin 5	Fenofibrate 67	60
	<i>Rosuvastatin 5-10</i>	<i>Fenofibrate 67</i>	113
Davidson (2001)¹⁸⁵	Lovastatin 10	NONE	26
	Lovastatin 10	C-lam 2300	23
	Lovastatin 10	C-lam 2300	27
	<i>Lovastatin 10</i>	<i>C-lam 2300</i>	50
Constance (2007)¹⁹⁴	Atorvastatin 20	NONE	219
	Simvastatin 20	Ezetimibe 10	220
	Simvastatin 40	Ezetimibe 10	222
	<i>Simvastatin 20-40</i>	<i>Ezetimibe 10</i>	442
Kos Pharm (MA- 14)¹⁰⁴	Lovastatin 40	NONE	33
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 40	Niacin (ER) 2500	32
	Lovastatin 10	Niacin (ER) 2500	34
	<i>Lovastatin 10</i>	<i>Niacin (ER) 2500</i>	100
Kos Pharm (MA- 06)¹⁰⁵	Lovastatin 40	NONE	61
	Lovastatin 20	Niacin (ER) 1000	57
	Lovastatin 40	Niacin (ER) 2000	57
	<i>Lovastatin 40</i>	<i>Niacin (ER) 1000-2000</i>	114
Ballantyne (2008)¹⁵⁰	Simvastatin 20	NONE	114
	Simvastatin 20	Niacin (ER) 1000	123
	Simvastatin 20	Niacin (ER) 2000	64
	<i>Simvastatin 20</i>	<i>Niacin (ER) 1000-2000</i>	187
Ballantyne (2008)¹⁷¹	Simvastatin 20	NONE	119
	Simvastatin 20	Niacin (ER) 1000	116
	Simvastatin 20	Niacin (ER) 2000	100
	<i>Simvastatin 20</i>	<i>Niacin (ER) 1000-2000</i>	216
All cause mortality - Lower dose statin plus nonstatin in combination compared with higher dose monotherapy using the same statin			
Durrington (2004)¹²⁵	Rosuvastatin 40	NONE	53
	Rosuvastatin 10	Fenofibrate 67	53
	Rosuvastatin 5	Fenofibrate 67	60
	<i>Rosuvastatin 5-10</i>	<i>Fenofibrate 67</i>	113
All-cause mortality in participants with diabetes mellitus			
Durrington (2004)¹²⁵	Rosuvastatin 40	NONE	53
	Rosuvastatin 10	Fenofibrate 67	53
	Rosuvastatin 5	Fenofibrate 67	60

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
	<i>Rosuvastatin 5-10</i>	<i>Fenofibrate 67</i>	113
Constance (2007)¹⁹⁴	Atorvastatin 20	NONE	219
	Simvastatin 40	Ezetimibe 10	222
	Simvastatin 20	Ezetimibe 10	220
	<i>Simvastatin 20-40</i>	<i>Ezetimibe 10</i>	<i>442</i>
Fatal myocardial infarction			
Kos Pharm (MA- 06)¹⁰⁵	Lovastatin 40	NONE	61
	Lovastatin 20	Niacin (ER) 1000	57
	Lovastatin 40	Niacin (ER) 2000	57
	<i>Lovastatin 40</i>	<i>Niacin (ER) 1000-2000</i>	114
Vascular death			
Hunninghake (2003)¹²⁸	Lovastatin 40	NONE	61
	Lovastatin 20	Niacin (ER) 1000	57
	Lovastatin 40	Niacin (ER) 2000	57
	<i>Lovastatin 40</i>	<i>Niacin (ER) 1000-2000</i>	114

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

Table E-2. Within-trial, within-treatment pooling of multiple treatment group data for surrogate outcomes

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
Achieving ATP III target			
Durrington (2004)¹²⁵	Rosuvastatin 40	NONE	50
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	53
	<i>Rosuvastatin 5-40</i>	<i>Fenofibrate 67</i>	113
Constance (2007)¹⁹⁴	Atorvastatin 20	NONE	219
	Simvastatin 40	Ezetimibe 10	220
	Simvastatin 20	Ezetimibe 10	222
	<i>Simvastatin 20-40</i>	<i>Ezetimibe 10</i>	442
Feldman (2004)⁴⁷	Simvastatin 40	NONE	248
	Simvastatin 10	Ezetimibe 10	245
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 40	Ezetimibe 10	97
	<i>Simvastatin 10-40</i>	<i>Ezetimibe 10</i>	451
Achieving ATP III targets - participants with CAD			
Bays (2003)⁴⁹	Atorvastatin 40	NONE	16
	Simvastatin 40	NONE	18
	<i>Mixed</i>	<i>NONE</i>	34
	Lovastatin 40	Niacin (ER) 2000	17
	Lovastatin 40	Niacin (ER) 1000	15
	<i>Lovastatin 40</i>	<i>Niacin (ER) 1000-2000</i>	32
Achieving ATP III targets - participants with diabetes mellitus			
Durrington (2004)¹²⁵	Rosuvastatin	NONE	50
	Rosuvastatin 10	Fenofibrate 67	50
	Rosuvastatin 5	Fenofibrate 67	60
	<i>Rosuvastatin 5-10</i>	<i>Fenofibrate 67</i>	110
Goldberg (2006)¹⁴⁴	Atorvastatin 20	NONE	240
	Atorvastatin 10	NONE	237
	<i>Atorvastatin</i>	<i>NONE</i>	241
	Simvastatin 10	Ezetimibe 10	242
	Simvastatin 10	Ezetimibe 10	238
	<i>Simvastatin 10</i>	<i>Ezetimibe 10</i>	480
Constance (2007)¹⁹⁴	Atorvastatin	NONE	219
	Simvastatin 10	Ezetimibe 10	222

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
Goldberg (2006) ¹⁴⁴	Simvastatin 10	Ezetimibe 10	220
	Simvastatin 10	Ezetimibe 10	442
	Atorvastatin 10	NONE	237
	Atorvastatin 20	NONE	240
	Atorvastatin 40	NONE	241
	<i>Atorvastatin 10-40</i>	<i>NONE</i>	<i>718</i>
	Simvastatin 20	Ezetimibe 10	238
	Simvastatin 40	Ezetimibe 10	242
LDL-c Feldman (2004) ⁴⁷	Simvastatin 40	NONE	248
	Simvastatin 40	Ezetimibe 10	97
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 10	<i>Ezetimibe 10</i>	<i>245</i>
	<i>Simvastatin 10-40</i>	<i>Ezetimibe 10</i>	<i>451</i>
Insull (2004) ¹⁸²	Lovastatin 40	NONE	33
	Lovastatin 40	Niacin (ER) 2500	32
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 10	Niacin (ER) 2500	34
	<i>Lovastatin 10-40</i>	<i>Niacin (ER) 2500</i>	<i>100</i>
Durrington (2004) ¹²⁵	Rosuvastatin 40	NONE	51
	Rosuvastatin 10	Fenofibrate 67	53
	Rosuvastatin 5	Fenofibrate 67	60
	<i>Rosuvastatin 5-10</i>	<i>Fenofibrate 67</i>	<i>113</i>
Capuzzi (2003) ¹⁵⁵	Rosuvastatin 40	NONE	46
	Rosuvastatin 10	Niacin (ER) 2000	78
	Rosuvastatin 40	Niacin (ER) 1000	71
	<i>Rosuvastatin 10-40</i>	<i>Niacin (ER) 1000-2000</i>	<i>71</i>
Gagne (2002) ¹³²	Atorvastatin 80	NONE	12
	Simvastatin 80	NONE	5
	<i>Mixed 80</i>	<i>NONE</i>	<i>17</i>
	Atorvastatin 40	Ezetimibe 10	12
	Simvastatin 40	Ezetimibe 10	4
	Atorvastatin 80	Ezetimibe 10	12
	Simvastatin 80	Ezetimibe 10	5
	<i>Mixed 40-80</i>	<i>Ezetimibe 10</i>	<i>33</i>
Hunninghake (2001) ¹³³	Atorvastatin 10	NONE	18
	Atorvastatin 80	NONE	20
	<i>Atorvastatin 10-80</i>	<i>NONE</i>	<i>38</i>
	Atorvastatin 10	C-lam 3800	18
Davidson (2001) ¹⁸⁵	Lovastatin 10	NONE	26
	Lovastatin 10	C-lam 2300	23
	Lovastatin 10	C-lam 2300	27

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
Knapp (2001) ¹⁷²	Lovastatin 10	C-lam 2300	50
	Simvastatin 20	C-lam 2300	37
	Simvastatin 10	C-lam 3800	34
	<i>Simvastatin 10-20</i>	<i>C-lam 2300-3800</i>	<i>71</i>
	Simvastatin 20	NONE	39
	Simvastatin 10	NONE	35
Sprecher (1994) ⁵²	Simvastatin 10-20	NONE	74
	Fluvastatin 20	NONE	38
	Fluvastatin 10	NONE	38
Sprecher (1994) ⁵²	<i>Fluvastatin 10-20</i>	<i>NONE</i>	<i>76</i>
	Fluvastatin 20	C-amine 16000	35
	Fluvastatin 10	C-amine 16000	35
PMSG II (1993) ¹⁹¹	<i>Fluvastatin 10-20</i>	<i>C-amine 16000</i>	<i>70</i>
	Pravastatin 80	NONE	62
	Pravastatin 40	NONE	57
Simons (1992) ¹⁷³	<i>Pravastatin 40-80</i>	<i>NONE</i>	<i>119</i>
	Pravastatin 40	C-amine 24000	61
	Simvastatin 40	NONE	22
	Simvastatin 40	C-pol 5000	19
	Simvastatin 40	C-pol 10000	20
	<i>Simvastatin 40</i>	<i>C-pol 5000-10000</i>	<i>39</i>
McKenney (2007_2) ¹³⁹	Rosuvastatin 40	NONE	73
	Atorvastatin 40	Niacin (ER) 2000	60
	Atorvastatin 20	Niacin (ER) 1000	65
Goldberg (2006) ¹⁴⁴	<i>Mixed 20-40</i>	<i>Niacin (ER) 1000-2000</i>	<i>125</i>
	Atorvastatin 20	NONE	240
	Atorvastatin 10	NONE	237
	Atorvastatin 40	NONE	241
	<i>Atorvastatin 10-40</i>	<i>NONE</i>	<i>718</i>
	Simvastatin 40	Ezetimibe 10	242
Constance (2007) ¹⁹⁴	Simvastatin 20	Ezetimibe 10	238
	<i>Simvastatin 20-40</i>	<i>Ezetimibe 10</i>	<i>480</i>
	Atorvastatin 20	NONE	213
Isaacsohn (1997) ¹⁶³	Simvastatin 40	Ezetimibe 10	215
	Simvastatin 20	Ezetimibe 10	210
	Simvastatin 20-40	<i>Ezetimibe 10</i>	<i>425</i>
	Atorvastatin 80	NONE	16
	Atorvastatin 40	C-pol 20000	11
	Simvastatin 40	C-pol 20000	10
	<i>Mixed 40</i>	<i>C-pol 20000</i>	<i>21</i>

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
Kos Pharm (MA-14) ¹⁰⁴	Lovastatin 40	NONE	29
	Lovastatin 40	Niacin (ER) 2500	23
	Lovastatin 20	Niacin (ER) 2500	24
	Lovastatin 10	Niacin (ER) 2500	30
	<i>Lovastatin 10-40</i>	<i>Niacin (ER) 2500</i>	<i>77</i>
Kos Pharm (MA-06) ¹⁰⁵	Lovastatin 40	NONE	53
	Lovastatin 20	Niacin (ER) 1000	40
	Lovastatin 40	Niacin (ER) 2000	42
	<i>Lovastatin 20-40</i>	<i>Niacin (ER) 1000-2000</i>	<i>82</i>
LDL-c - Lower dose statin plus nonstatin in combination compared with higher dose monotherapy using the same statin			
Durrington (2004) ¹²⁵	Rosuvastatin 40	NONE	51
	Rosuvastatin 10	Fenofibrate 67	53
	Rosuvastatin 5	Fenofibrate 67	60
	<i>Rosuvastatin 5-10</i>	<i>Fenofibrate 67</i>	<i>113</i>
Feldman (2004) ⁴⁷	Simvastatin 40	NONE	248
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 10	<i>Ezetimibe 10</i>	<i>245</i>
	<i>Simvastatin 10-20</i>	<i>Ezetimibe 10</i>	<i>451</i>
LDL-c – high risk participants			
Feldman (2004) ⁴⁷	Simvastatin 40	NONE	248
	Simvastatin 40	Ezetimibe 10	97
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 10	<i>Ezetimibe 10</i>	<i>245</i>
	<i>Simvastatin 10-40</i>	<i>Ezetimibe 10</i>	<i>451</i>
LDL-c - Lower dose statin plus nonstatin in combination compared with higher dose monotherapy using the same statin in high risk participants			
Feldman (2004) ⁴⁷	Simvastatin 40	NONE	248
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 10	<i>Ezetimibe 10</i>	<i>245</i>
	<i>Simvastatin 10-20</i>	<i>Ezetimibe 10</i>	<i>451</i>
HDL-c			
Feldman (2004) ⁴⁷	Simvastatin 20	NONE	248
	Simvastatin 10	Ezetimibe 10	245
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 40	Ezetimibe 10	97
	<i>Simvastatin 10-40</i>	<i>Ezetimibe 10</i>	<i>451</i>

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
Insull (2004) ¹⁸²	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) ¹²⁵	Rosuvastatin 40	NONE	51
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	53
	Rosuvastatin 5-10	Fenofibrate 67	113
Capuzzi (2003) ¹⁵⁵	Rosuvastatin 40	NONE	46
	Rosuvastatin 10	Niacin (ER) 2000	78
	Rosuvastatin 40	Niacin (ER) 1000	71
	<i>Rosuvastatin 10-40</i>	<i>Niacin (ER) 1000-2000</i>	198
Davidson (2001) ¹⁸⁵	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) ¹⁹¹	Pravastatin 80	NONE	62
	Pravastatin 40	NONE	57
	Pravastatin 40	NONE	119
	Pravastatin 40	C-amine 24000	61
Simons (1992) ¹⁷³	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) ¹³⁹	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) ¹⁹⁴	Atorvastatin 20	NONE	218
	Simvastatin 40	Ezetimibe 10	220
	Simvastatin 20	Ezetimibe 10	219
	Simvastatin 20-40	Ezetimibe 10	439
Isaacsohn (1997) ¹⁶³	Atorvastatin 80	NONE	16
	Simvastatin 40	C-pol 20000	10
	Atorvastatin 40	C-pol 20000	11
	Mixed 40	C-pol 20000	21

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
Kos Pharm (MA-14) ¹⁰⁴	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) ¹⁰⁵	Lovastatin 40	NONE	53
	Lovastatin 20	Niacin (ER) 1000	40
	Lovastatin 40	Niacin (ER) 2000	42
	<i>Lovastatin 40</i>	<i>Niacin (ER) 1000-2000</i>	<i>82</i>
HDL-c - Lower dose statin plus nonstatin in combination compared with higher dose monotherapy using the same statin			
Durrington (2004) ¹²⁵	Rosuvastatin 40	NONE	51
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	53
	Rosuvastatin 5-10	Fenofibrate 67	113
HDL-c – high risk participants			
Goldberg (2006) ¹⁴⁴	Atorvastatin 10	NONE	237
	Atorvastatin 20	NONE	240
	Atorvastatin 40	NONE	241
	<i>Atorvastatin 10-40</i>	<i>NONE</i>	<i>718</i>
	Simvastatin 20	Ezetimibe 10	238
	Simvastatin 40	Ezetimibe 10	242
	<i>Simvastatin 20-40</i>	<i>Ezetimibe 10</i>	<i>480</i>
HDL-c – participants with diabetes mellitus			
Goldberg (2006) ¹⁴⁴	Atorvastatin 10	NONE	237
	Atorvastatin 20	NONE	240
	Atorvastatin 40	NONE	241
	<i>Atorvastatin 10-40</i>	<i>NONE</i>	<i>718</i>
	Simvastatin 20	Ezetimibe 10	238
	Simvastatin 40	Ezetimibe 10	242
	<i>Simvastatin 20-40</i>	<i>Ezetimibe 10</i>	<i>480</i>
Total cholesterol: HDL-c ratio			
Durrington (2004) ¹²⁵	Rosuvastatin 40	NONE	51
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	53
	<i>Rosuvastatin 5-40</i>	<i>Fenofibrate 67</i>	<i>113</i>

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
McKenney (2007_2) ¹³⁹	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) ¹⁹⁴	Atorvastatin 20	NONE	218
	Simvastatin 40	Ezetimibe 10	220
	Simvastatin 20	Ezetimibe 10	219
	Simvastatin 20-40	Ezetimibe 10	439
Goldberg (2006) ¹⁴⁴	Atorvastatin 10	NONE	237
	Atorvastatin 20	NONE	240
	Atorvastatin 40	NONE	241
	Atorvastatin 10-40	NONE	718
	Simvastatin 20	Ezetimibe 10	238
	Simvastatin 40	Ezetimibe 10	242
	Simvastatin 20-40	Ezetimibe 10	480
	Total cholesterol: HDL-c ratio – high risk participants		
Goldberg (2006) ¹⁴⁴	Atorvastatin 10	NONE	237
	Atorvastatin 20	NONE	240
	Atorvastatin 40	NONE	241
	Atorvastatin 10-40	NONE	718
	Simvastatin 20	Ezetimibe 10	238
	Simvastatin 40	Ezetimibe 10	242
	Simvastatin 20-40	Ezetimibe 10	480
	Total cholesterol: HDL-c ratio – participants with diabetes mellitus		
Goldberg (2006) ¹⁴⁴	Atorvastatin 10	NONE	237
	Atorvastatin 20	NONE	240
	Atorvastatin 40	NONE	241
	Atorvastatin 10-40	NONE	718
	Simvastatin 20	Ezetimibe 10	238
	Simvastatin 40	Ezetimibe 10	242
	Simvastatin 20-40	Ezetimibe 10	480

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

Table E-3. Within-trial, within-treatment pooling of multiple treatment group data for adverse events and treatment adherence

Outcome / Trial	Statin Dose (mg/day)	Non-statin drug Dose (mg/day)	Number of participants
Cancer			
Kos Pharm (MA-06)¹⁰⁵	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			
Feldman (2004)⁴⁷	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
Durrington (2004)¹²⁵	Rosuvastatin 40	NONE	53
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	55
	Rosuvastatin 5-10	Fenofibrate 67	115
Capuzzi (2003)¹⁵⁵	Rosuvastatin 40	NONE	46
	Rosuvastatin 10	Niacin (ER) 2000	80
	Rosuvastatin 40	Niacin (ER) 1000	72
	Rosuvastatin 10-40	Niacin (ER) 1000-2000	152
McKenney (2007)¹³⁹	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
Kos Pharm (MA-14)¹⁰⁴	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
Kos Pharm (MA-06)¹⁰⁵	Lovastatin 40	NONE	61
	Lovastatin 20	Niacin (ER) 1000	57
	Lovastatin 40	Niacin (ER) 2000	57
	Lovastatin 40	Niacin (ER) 1000-2000	114
CPK above 10 times the upper limit of normal - Lower dose statin plus nonstatin in combination compared with higher dose monotherapy using the same statin			
Feldman (2004)⁴⁷	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
Durrington (2004)¹²⁵	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 Feldman (2004) ⁴⁷	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
Insull (2004) ¹⁸²	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
Durrington (2004) ¹²⁵	Rosuvastatin 40	NONE	53
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	55
	Rosuvastatin 5-10	Fenofibrate 67	115
Capuzzi (2003) ¹⁵⁵	Rosuvastatin 40	NONE	46
	Rosuvastatin 10	Niacin (ER) 2000	80
	Rosuvastatin 40	Niacin (ER) 1000	72
	Rosuvastatin 10-40	Niacin (ER) 1000-2000	152
Hunninghake (2003) ¹²⁸	Lovastatin 40	NONE	61
	Lovastatin 20	Niacin (ER) 1000	57
	Lovastatin 40	Niacin (ER) 2000	57
	Lovastatin 20-40	Niacin (ER) 1000-2000	114
Athyros (2001) ⁵⁰	Atorvastatin 20	NONE	131
	Pravastatin 20	Gemfibrozil 1200	133
	Simvastatin 20	Gemfibrozil 1200	129
	Mixed 20	Gemfibrozil 1200	262
Davidson (2001) ¹⁸⁵	Lovastatin 10	NONE	26
	Lovastatin 10	C-lam 2300	23
	Lovastatin 10	C-lam 2300	27
	Lovastatin 10	C-lam 300	50
Constance (2007) ¹⁹⁴	Atorvastatin 20	NONE	219
	Simvastatin 20	Ezetimibe 10	220
	Simvastatin 40	Ezetimibe 10	222
	Simvastatin 20-40	Ezetimibe 10	442
Kos Pharm (MA- 14) ¹⁰⁴	Lovastatin 40	NONE	33
	Lovastatin 10	Niacin (ER) 2500	34
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 40	Niacin (ER) 2500	32
Ballantyne (2008_a) ¹⁵⁰	Lovastatin 10-40	Niacin (ER) 2500	100
	Simvastatin 20	NONE	114
	Simvastatin 20	Niacin (ER) 1000	123
	Simvastatin 20	Niacin (ER) 2000	64
Ballantyne (2008_b) ¹⁷¹	Simvastatin 20	Niacin (ER) 1000-2000	187
	Simvastatin 20	NONE	119
	Simvastatin 20	Niacin (ER) 1000	116
	Simvastatin 20	Niacin (ER) 2000	100
	Simvastatin 20	Niacin (ER) 1000-2000	216

Elevated serum AST, ALT or hepatitis - Lower dose statin plus nonstatin in combination compared with higher dose monotherapy using the same statin

Feldman (2004)⁴⁷	Simvastatin 40	NONE	248
	Simvastatin 10	Ezetimibe 10	245
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 40	Ezetimibe 10	97
Durrington (2004)¹²⁵	Simvastatin 10-40	Ezetimibe 10	451
	Rosuvastatin 40	NONE	53
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	55
Myalgia Kosoglou (2004-b)¹⁸¹	Rosuvastatin 5-10	Fenofibrate 67	115
	Lovastatin 20	NONE	8
	Lovastatin 20	Ezetimibe 10	8
	Lovastatin 40	Ezetimibe 10	7
Durrington (2004)¹²⁵	Lovastatin 20-40	Ezetimibe 10	15
	Rosuvastatin 40	NONE	53
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	55
Capuzzi (2003)¹⁵⁵	Rosuvastatin 5-10	Fenofibrate 67	115
	Rosuvastatin 40	NONE	46
	Rosuvastatin 10	Niacin (ER) 2000	80
	Rosuvastatin 40	Niacin (ER) 1000	72
Athyros (2001)⁵⁰	Rosuvastatin 10-40	Niacin (ER) 1000-2000	152
	Atorvastatin 20	NONE	131
	Simvastatin 20	Gemfibrozil 1200	129
	Pravastatin 20	Gemfibrozil 1200	133
Davidson (2001)¹⁸⁵	Mixed 20	Gemfibrozil 1200	262
	Lovastatin 10	NONE	26
	Lovastatin 10	C-lam 2300	27
	Lovastatin 10	C-lam 2300	23
Myalgia - Lower dose statin plus nonstatin in combination compared with higher dose monotherapy using the same statin	Lovastatin 10	C-lam 2300	50
	Rosuvastatin 40	NONE	53
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	55
Rhabdomyolysis Feldman (2004)⁴⁷	Rosuvastatin 5-10	Fenofibrate 67	115
	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

Kos Pharm (MA-14)¹⁰⁴	Lovastatin 40	NONE	33
	Lovastatin 10	Niacin (ER) 2500	34
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 40	Niacin (ER) 2500	32
	<i>Lovastatin 10-40</i>	<i>Niacin (ER) 2500</i>	<i>100</i>
Ballantyne (2008_a)¹⁵⁰	Simvastatin 20	NONE	114
	Simvastatin 20	Niacin (ER) 1000	123
	Simvastatin 20	Niacin (ER) 2000	64
	<i>Simvastatin 20</i>	<i>Niacin (ER) 1000-2000</i>	<i>187</i>
Ballantyne (2008_b)¹⁷¹	Simvastatin 20	NONE	119
	Simvastatin 20	Niacin (ER) 1000	116
	Simvastatin 20	Niacin (ER) 2000	100
	<i>Simvastatin 20</i>	<i>Niacin (ER) 1000-2000</i>	<i>216</i>

Rhabdomyolysis - Lower dose statin plus nonstatin in combination compared with higher dose monotherapy using the same statin

Feldman (2004)⁴⁷	Simvastatin 40	NONE	253
	Simvastatin 10	Ezetimibe 10	251
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 40	Ezetimibe 10	97
	<i>Simvastatin 10-40</i>	<i>Ezetimibe 10</i>	<i>457</i>

Serious adverse events

Feldman (2004)⁴⁷	Simvastatin 40	NONE	253
	Simvastatin 10	Ezetimibe 10	251
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 40	Ezetimibe 10	97
	<i>Simvastatin 10-40</i>	<i>Ezetimibe 10</i>	<i>457</i>
Kos Pharm (MA-14)¹⁰⁴	Lovastatin 40	NONE	33
	Lovastatin 10	Niacin (ER) 2500	34
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 40	Niacin (ER) 2500	32
	<i>Lovastatin 10-40</i>	<i>Niacin (ER) 2500</i>	<i>100</i>
Ballantyne (2008_a)¹⁵⁰	Simvastatin 20	NONE	114
	Simvastatin 20	Niacin (ER) 1000	123
	Simvastatin 20	Niacin (ER) 2000	64
	<i>Simvastatin 20</i>	<i>Niacin (ER) 1000-2000</i>	<i>187</i>
Ballantyne (2008_b)¹⁷¹	Simvastatin 20	NONE	119
	Simvastatin 20	Niacin (ER) 1000	116
	Simvastatin 20	Niacin (ER) 2000	100
	<i>Simvastatin 20</i>	<i>Niacin (ER) 1000-2000</i>	<i>216</i>

Serious adverse events - Lower dose statin plus nonstatin in combination compared with higher dose monotherapy using the same statin

Feldman (2004)⁴⁷	Simvastatin 40	NONE	253
	Simvastatin 10	Ezetimibe 10	251
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 40	Ezetimibe 10	97
	<i>Simvastatin 10-40</i>	<i>Ezetimibe 10</i>	<i>457</i>

Total adverse events

Feldman (2004)⁴⁷	Simvastatin 40	NONE	253
	Simvastatin 10	Ezetimibe 10	251
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 40	Ezetimibe 10	97

	<i>Simvastatin 10-40</i>	<i>Ezetimibe 10</i>	457
Insull (2004)¹⁸²	Lovastatin 40	NONE	33
	Lovastatin 10	Niacin (ER) 2500	34
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 40	Niacin (ER) 2500	32
	<i>Lovastatin 10-40</i>	<i>Niacin (ER) 2500</i>	100
Durrington (2004)¹²⁵	Rosuvastatin 40	NONE	53
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	55
	<i>Rosuvastatin 5-10</i>	<i>Fenofibrate 67</i>	115
Capuzzi (2003)¹⁵⁵	Rosuvastatin 40	NONE	46
	Rosuvastatin 10	Niacin (ER) 2000	80
	Rosuvastatin 40	Niacin (ER) 1000	72
	<i>Rosuvastatin 10-40</i>	<i>Niacin (ER) 1000-2000</i>	152
Johansson (1995)¹³⁷	Simvastatin 40	NONE	26
	Simvastatin 20	C-pol 5000	29
	Simvastatin 20	C-pol 10000	28
	<i>Simvastatin 20</i>	<i>C-pol 5000-10000</i>	57
Kos Pharm (MA-14)¹⁰⁴	Lovastatin 40	NONE	33
	Lovastatin 10	Niacin (ER) 2500	34
	Lovastatin 20	Niacin (ER) 2500	34
	Lovastatin 40	Niacin (ER) 2500	32
	<i>Lovastatin 10-40</i>	<i>Niacin (ER) 2500</i>	100
Kos Pharm (MA-06)¹⁰⁵	Lovastatin 40	NONE	61
	Lovastatin 20	Niacin (ER) 1000	57
	Lovastatin 40	Niacin (ER) 2000	57
	<i>Lovastatin 20-40</i>	<i>Niacin (ER) 1000-2000</i>	114
Ballantyne (2008_a)¹⁵⁰	Simvastatin 20	NONE	114
	Simvastatin 20	Niacin (ER) 1000	123
	Simvastatin 20	Niacin (ER) 2000	64
	<i>Simvastatin 20</i>	<i>Niacin (ER) 1000-2000</i>	187
Ballantyne (2008_b)¹⁷¹	Simvastatin 20	NONE	119
	Simvastatin 20	Niacin (ER) 1000	116
	Simvastatin 20	Niacin (ER) 2000	100
	<i>Simvastatin 20</i>	<i>Niacin (ER) 1000-2000</i>	216
Total adverse events - Lower dose statin plus nonstatin in combination compared with higher dose monotherapy using the same statin			
Feldman (2004)⁴⁷	Simvastatin 40	NONE	253
	Simvastatin 10	Ezetimibe 10	251
	Simvastatin 20	Ezetimibe 10	109
	Simvastatin 40	Ezetimibe 10	97
	<i>Simvastatin 10-40</i>	<i>Ezetimibe 10</i>	457
Durrington (2004)¹²⁵	Rosuvastatin 40	NONE	53

Johansson (1995) ¹³⁷	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	55
	Rosuvastatin 5-10	Fenofibrate 67	115
	Simvastatin 40	NONE	26
	Simvastatin 20	C-pol 5000	29
	Simvastatin 20	C-pol 10000	28
Treatment Adherence			
Capuzzi (2003) ¹⁵⁵	Rosuvastatin 40	NONE	46
	Rosuvastatin 10	Niacin (ER) 2000	80
	Rosuvastatin 40	Niacin (ER) 1000	72
Hunninghake (2001) ¹³³	Rosuvastatin 10-40	Niacin (ER) 1000-2000	152
	Atorvastatin 10	NONE	19
	Atorvastatin 80	NONE	20
	Atorvastatin 10-80	NONE	39
	Atorvastatin 10	C-lam 3800	19
Eriksson (1998) ¹⁹⁰	Pravastatin 20	NONE	403
	Pravastatin 40	NONE	409
	Pravastatin 20-40	NONE	812
	Pravastatin 20	chlestyramine 8000	261
Johansson (1995) ¹³⁷	Simvastatin 40	NONE	26
	Simvastatin 20	C-pol 5000	29
	Simvastatin 20	C-pol 10000	28
	Simvastatin 20	C-pol 5000-10000	57
McKenney (2007) ¹³⁹	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 - Lower dose statin plus nonstatin in combination compared with higher dose monotherapy using the same statin			
Johansson (1995) ¹³⁷	Simvastatin 40	NONE	26
	Simvastatin 20	C-pol 5000	29
	Simvastatin 20	C-pol 10000	28
	Simvastatin 20	C-pol 5000-10000	57
Withdrawal due to adverse events			
Feldman (2004) ⁴⁷	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
Durrington (2004) ¹²⁵	Rosuvastatin 40	NONE	53
	Rosuvastatin 5	Fenofibrate 67	60
	Rosuvastatin 10	Fenofibrate 67	55

	Rosuvastatin 5-10	Fenofibrate 67	115
Gagne (2002)¹³²	Mixed 80	NONE	17
	Mixed 40	Ezetimibe 10	16
	Mixed 80	Ezetimibe 10	17
	Mixed 40-80	Ezetimibe 10	33
Athyros (2001)⁵⁰	Atorvastatin 20	NONE	134
	Simvastatin 20	Gemfibrozil 1200	136
	Pravastatin 20	Gemfibrozil 1200	135
	Mixed 20	Gemfibrozil 1200	271
Hunninghake (2001)¹³³	Atorvastatin 10	NONE	19
	Atorvastatin 80	NONE	20
	Atorvastatin 10-80	NONE	39
	Atorvastatin 10	C-lam 3800	19
Davidson (2001)¹⁸⁵	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)¹⁹¹	Pravastatin 40	NONE	63
	Pravastatin 80	NONE	63
	Pravastatin 40-80	NONE	126
	Pravastatin 40	chlestyramine 24000	64
Constance (2007)¹⁹⁴	Atorvastatin 20	NONE	219
	Simvastatin 20	Ezetimibe 10	220
	Simvastatin 40	Ezetimibe 10	222
	Simvastatin 20-40	Ezetimibe 10	442
Kos Pharm (MA-14)¹⁰⁴	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
Kos Pharm (MA-06)¹⁰⁵	Lovastatin 40	NONE	61
	Lovastatin 20	Niacin (ER) 1000	57
	Lovastatin 40	Niacin (ER) 2000	57
	Lovastatin 20-40	Niacin (ER) 1000-2000	114
Ballantyne (2008_a)¹⁵⁰	Simvastatin 20	NONE	114
	Simvastatin 20	Niacin (ER) 1000	123
	Simvastatin 20	Niacin (ER) 2000	64
	Simvastatin 20	Niacin (ER) 1000-2000	187
Ballantyne (2008_b)¹⁷¹	Simvastatin 20	NONE	119
	Simvastatin 20	Niacin (ER) 1000	116
	Simvastatin 20	Niacin (ER) 2000	100
	Simvastatin 20	Niacin (ER) 1000-2000	216
Withdrawal due to adverse events - Lower dose statin plus nonstatin in combination compared with higher dose monotherapy using the same statin			
Feldman (2004)⁴⁷	Simvastatin 40	NONE	253

Durrington
(2004)¹²⁵

Simvastatin 10	Ezetimibe 10	251
Simvastatin 20	Ezetimibe 10	109
Simvastatin 40	Ezetimibe 10	97
<i>Simvastatin 10-40</i>	<i>Ezetimibe 10</i>	<i>457</i>
Rosuvastatin 40	NONE	53
Rosuvastatin 5	Fenofibrate 67	60
Rosuvastatin 10	Fenofibrate 67	55
<i>Rosuvastatin 5-10</i>	<i>Fenofibrate 67</i>	<i>115</i>

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

Appendix F: 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

This set of tables present all the randomized controlled trial data employed in evidence synthesis. The data falls into one or more of the following categories for the outcomes:

- All statins, all doses, all clinical populations. These are clinically diverse trials, to investigate a common drug effect. This category includes analyses for all types of statin, comparing similar or closest possible statin doses in the two investigated interventions (i.e. statin-ezetimibe combination therapy, and statin monotherapy). It includes trials of any duration – short-term trials of less than 24 weeks duration, and long-term trials of 24 weeks or longer follow-up. It includes trials with inadequate, unclear or adequate allocation concealment.
- All statins, lower versus higher doses, all clinical populations. These are clinically diverse trials to investigate a potential advantage of higher dose statin monotherapy over combination therapy with a lower dose of the same statin plus ezetimibe. In other words, this category includes statin specific analyses comparing lower doses of statin-ezetimibe combination with a higher dose of the same statin monotherapy. It includes trials of any duration – short-term trials of less than 24 weeks duration, and long-term trials of 24 weeks or longer follow-up. It includes trials with inadequate, unclear or adequate allocation concealment.
- All statins, all doses, intensive lipid lowering populations and clinical subgroups. These are a variety of relatively clinically homogenous populations, to investigate effects among specific groups within clinical diversity. This category includes statin non-specific analyses comparing similar or closest possible statin doses in the two investigated interventions (i.e. statin-ezetimibe combination, and statin monotherapy). It includes trials of any duration – short-term trials of less than 24 weeks duration, and long-term trials of 24 weeks or longer follow-up. It includes trials with inadequate, unclear or adequate allocation concealment.

- All statins, lower versus higher doses, intensive lipid lowering populations and clinical subgroups. These are a variety of relatively clinically homogenous populations, to investigate potential advantage of higher dose statin monotherapy over combination therapy with a lower dose of the same statin plus ezetimibe, among diverse clinical subgroups. This category includes statin specific analyses comparing lower doses of statin-ezetimibe combination therapy with a higher dose of the same statin monotherapy. It includes trials of any duration – short-term trials of less than 24 weeks duration, and long-term trials of 24 weeks or longer follow-up. It includes trials with inadequate, unclear or adequate allocation concealment.
- **Note, when all the trial data in a category is included as a whole in a prior category, then that category is not reported in the appendix. Also adverse event outcomes were assessed in all trial populations and not specific clinical groups. Non-HDL-c and triglycerides were investigated in the diabetes mellitus subgroup only – no evidence was available for triglycerides**

Table F-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 statins, all doses, all clinical populations											
Ballantyne (2003) ¹²⁶ Ezetimibe Study Group International Pharm. Fund Multicentre	1° HC, heterogeneous 10-year CHD risk estimates	Atorvastatin 80	201	Atorvastatin 80	45	52	183	0/0	unclear	2	No
Goldberg (2004) ⁴⁸ Ezetimibe Study Group International Pharm. fund	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	539	Simvastatin 20-80	229	48	175	0/0	Adequate	5	No
Landray (2006) ¹⁶⁶ 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 7.86 (0.81, 76.45)	Adequate	2	Yes
Gaudiani (2005) ¹²¹ 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
Rodney (2006) ¹¹¹ Pharm. Fund Multicentre	African descent, 1° HC	Simvastatin 20	124	Simvastatin 20	123	12	176	0/0	Adequate	5	No
Melani (2003) ¹²⁷ Ezetimibe Study Group North America Pharm. Fund Multicentre	1° HC, heterogeneous 10-year CHD risk estimates	Pravastatin 10-40	184	Pravastatin 10-40	192	12	178	0/0	Adequate	4	Yes
Kerzner (2003) ¹²⁹ Ezetimibe Study Group North America Pharm. Fund Multicentre	1° HC, heterogeneous 10-year CHD risk estimates	Lovastatin 10-40	192	Lovastatin 10-40	220	12	179	0/0	unclear	3	Yes
Constance (2007) ¹⁹⁴ International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	442	Atorvastatin 20	219	8	94	1/1 0.47 (0.02, 8.88)	Adequate	3	No
Farnier (2005) ¹¹⁴ 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) ¹¹⁵ International Pharm. Fund Multicentre	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	220	Atorvastatin 10-20	230	6	122	0/1 0.14 (0.00, 7.13)	unclear	4	No
Brohet (2005) ¹¹⁶ 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) ¹¹⁷ 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	Adequate	4	No
Blagden (2007) ¹⁴⁰ Europe Pharm. Fund Multicentre	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	0/0	unclear	4	Yes
Ballantyne (2007) ¹⁴² Europe Pharm. Fund Multicentre	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	190	1/0 7.14 (0.14, 360.28)	unclear	1	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
Patel (2006) ¹⁴³ Europe Pharm. Fund Multicentre	Participants with CAD not on recent lipid lowering drug treatment	Simvastatin 20	76	Simvastatin 20	75	6	160	0/1 0.13 (0.00, 6.73)	unclear	3	No
Goldberg (2006) ¹⁴⁴ 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 0.19 (0.00, 10.19)	Adequate	3	No
Catapano (2006_1) ¹⁹³ North America Pharm. Fund Multicentre	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Simvastatin 20	492	Rosuvastatin 10	492	6	173	0/0	Adequate	3	No
Catapano (2006_2) ¹⁹³ North America Pharm. Fund Multicentre	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Simvastatin 40	493	Rosuvastatin 20	495	6	173	0/0	Adequate	3	No
Catapano (2006_3) ¹⁹³ North America Pharm. Fund Multicentre	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Simvastatin 80	493	Rosuvastatin 40	494	6	173	0/0	Adequate	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
Reckless (2008) ¹⁴⁹ INFORCE International Pharm. Fund Multicentre	CHD patients on previous stable statin dose	Simvastatin 40	213	Double the previous (mixed) statin dose	211	12	92.5	4/4 0.99 (0.24, 4.01)	Adequate	2	No
Roeters van Lennep (2008) ¹⁵¹ EASEGO Europe Pharm. Fund Multicentre	CHD and/or controlled type II DM patients not on target LDL-c despite prior low dose simvastatin or atorvastatin therapy	Simvastatin 40	178	Simvastatin 40 or Atorvastatin 20	189	12	115	0/0	Unclear	3	No
Gouni-Berthold (2008) ¹¹⁰ Europe Pharm. Fund Single	Healthy males with LDL-c < 190 mg/dL and < 60 years of age, previously not on lipid lowering treatment	Simvastatin 40	24	Simvastatin 40	24	2	114.5	0/0	Unclear	2	Yes
Conrad (2008) ¹⁵⁸ International Pharm. Fund Multicenter	Moderately high risk participants on atorvastatin 20 mg/day or statin naive and with LDL-c 100 mg/dL to ≤ 160 mg/dL	Atorvastatin 20	96	Atorvastatin 40	98	6	119	0/0	Adequate	5	No
Leiter (2008) ¹⁵⁹ North America Pharm. Fund Multicenter	Participants with or without prior lipid lowering therapy with 10-year CHD risk > 20%	Atorvastatin 40	286	Atorvastatin 80	289	6	89	0/0	Adequate	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
Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c \geq 130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	34	Simvastatin 40	66	4	169	0/0	Adequate	5	Yes
Ballantyne (2005) ¹¹⁸ VYVA North America Pharm. Fund Multicenter	Participants with DM not at LDL-c ATP III goal off lipid lowering treatment	Simvastatin 10-80	220	Atorvastatin 10-80	206	6	178	0/1 0.13 (0.00, 6.39)	Adequate	2	No
All-cause Mortality: all statins, lower versus higher doses, all clinical populations											
Conrad (2008) ¹⁵⁸ International Pharm. Fund Multicenter	Moderately high risk participants on atorvastatin 20 mg/day or statin naive and with LDL-c 100 mg/dL to \leq 160 mg/dL	Atorvastatin 20	96	Atorvastatin 40	98	6	119	0/0	Adequate	5	No
Gaudiani (2005) ¹²¹ 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
Roeters van Lennep (2008) ¹⁵¹ EASEGO Europe Pharm. Fund Multicentre	CHD and/or controlled type II DM patients not on target LDL-c despite prior low dose simvastatin or atorvastatin therapy	Simvastatin 20	110	Simvastatin 40	115	12	115	0/0	Unclear	3	No
Dobs (2003) ¹⁶⁹ Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c \geq 130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	34	Simvastatin 40	66	4	169	0/0	Adequate	5	Yes
All-cause mortality: all statins, all doses, intensive lipid lowering populations and clinical subgroups											
Farnier (2005) ¹¹⁴ 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) ¹¹⁵ International Pharm. Fund Multicentre	Participants with CAD on low dose atorvastatin	Atorvastatin 10-20	220	Atorvastatin 10-20	230	6	122	0/1 0.14 (0.00, 7.13)	unclear	4	No
Brohet (2005) ¹¹⁶ 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

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) ¹²¹ 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) ¹⁴⁰ Europe Pharm. Fund Multicentre	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	0/0	unclear	4	Yes
Ballantyne (2007) ¹⁴² Europe Pharm. Fund Multicentre	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	190	1/0 7.14 (0.14, 360.28)	unclear	1	No
Patel (2006) ¹⁴³ Europe Pharm. Fund Multicentre	Participants with CAD not on recent lipid lowering drug treatment	Simvastatin 20	76	Simvastatin 20	75	6	160	0/1 0.13 (0.00, 6.73)	unclear	3	No
Goldberg (2006) ¹⁴⁴ 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 0.19 (0.00, 10.19)	Adequate	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) ¹⁹⁴ International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	442	Atorvastatin 20	219	8	94	1/1 0.47 (0.02, 8.88)	Adequate	3	No
Reckless (2008) ¹⁴⁹ INFORCE International Pharm. Fund Multicentre	CHD patients on previous stable statin dose	Simvastatin 40	213	Double the previous (mixed) statin dose	211	12	92.5	4/4 0.99 (0.24, 4.01)	Adequate	2	No
Roeters van Lennep (2008) ¹⁵¹ EASEGO Europe Pharm. Fund Multicentre	CHD and/or controlled type II DM patients not on target LDL-c despite prior low dose simvastatin or atorvastatin therapy	Simvastatin 40	178	Simvastatin 40 or Atorvastatin 20	189	12	115	0/0	Unclear	3	No
Leiter (2008) ¹⁵⁹ North America Pharm. Fund Multicenter	Participants with or without prior lipid lowering therapy with 10-year CHD risk > 20%	Atorvastatin 40	286	Atorvastatin 80	289	6	89	0/0	Adequate	5	No
Ballantyne (2005) ¹¹⁸ VYVA North America Pharm. Fund Multicenter	Participants with DM not at LDL-c ATP III goal off lipid lowering treatment	Simvastatin 10-80	220	Atorvastatin 10-80	206	6	178	0/1 0.13 (0.00, 6.39)	Adequate	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
Catapno (2006) ¹⁹³ North America Pharm. Fund Multicenter	Participants with DM	Simvastatin 20	190	Rosuvastatin 10	185	6	173	0/0	Adequate	3	No
Rodney (2006) ¹¹¹ Pharm. Fund Multicentre	African descent, 1° HC	Simvastatin 20	124	Simvastatin 20	123	12	176	0/0	Adequate	5	No
Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c \geq 130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	29	Simvastatin 40	15	4	169	0/0	Adequate	5	Yes
Reckless (2008) ¹⁴⁹ INFORCE International Pharm. Fund Multicentre	CHD patients on previous stable statin dose	Simvastatin 40	43	Double the previous (mixed) statin dose	41	12	92.5	1/1 0.95 (0.06, 15.75)	Adequate	2	No
All-cause mortality: all statins, lower versus higher doses, intensive lipid lowering populations and clinical subgroups											
Gaudiani (2005) ¹²¹ 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
Roeters van Lennep (2008) ¹⁵¹ EASEGO Europe Pharm. Fund Multicentre	CHD and/or controlled type II DM patients not on target LDL-c despite prior low dose simvastatin or atorvastatin therapy	Simvastatin 20	110	Simvastatin 40	115	12	115	0/0	Unclear	3	No
Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c \geq 130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	29	Simvastatin 40	15	4	169	0/0	Adequate	5	Yes
Vascular Death: all statins, all doses, all clinical populations											
Kastelein (2008) ⁴² ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	2/1 1.98 (0.21, 19.14)	Adequate	3	No
Davidson (2002_1) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicentre	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	61	Simvastatin 10	61	12	179	0/0	Adequate	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_2) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicentre	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	58	Simvastatin 20	53	12	179	1/0 6.78 (0.13, 342.99)	Adequate	4	No
Davidson (2002_3) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicentre	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 40	68	Simvastatin 40	60	12	179	0/0	Adequate	4	No
Davidson (2002_4) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicentre	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 80	52	Simvastatin 80	63	12	179	0/0	Adequate	4	No

Trial	Population	Combination Statin Dose (mg/day)	Combo N	Monotheapy 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 statins, lower versus higher doses, all clinical populations											
Davidson (2002_5) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicentre	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	61	Simvastatin 40	60	12	179	0/0	Adequate	4	No
Davidson (2002_6) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicentre	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	58	Simvastatin 80	63	12	179	1/0 8.05 (0.16, 407.27)	Adequate	4	No
Vascular death: all statins, all doses, intensive lipid lowering populations and clinical subgroups											
Kastelein (2008) ⁴² ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	2/1 1.98 (0.21, 19.14)	Adequate	3	No
Fatal Myocardial Infarction: all statins, all doses, all clinical populations											
Ballantyne (2007) ¹⁴² Europe Pharm. Fund Multicentre	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	190	1/0 7.14(0.14, 360.28)	unclear	1	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
Stein (2004) ¹⁵⁶ International Pharm. fund	Those with LDL \geq 130 mg/dL despite diet and atorvastatin 10 mg/day	Atorvastatin 40	278	Atorvastatin 80	290	14	186	0/1 0.14 (0.00, 7.11)	unclear	3	Yes
Reckless (2008) ¹⁴⁹ INFORCE International Pharm. Fund Multicentre	CHD patients on previous stable statin dose	Simvastatin 40	213	Double doses of pervious statins (mixed)	211	12	92.5	2/0 7.35 (0.46, 117.97)	Adequate	2	No
Any or unspecified myocardial infarction: all statins, all doses, all clinical populations											
Reckless (2008) ¹⁴⁹ INFORCE International Pharm. Fund Multicentre	CHD patients on previous stable statin dose	Simvastatin 40	213	Double doses of pervious statins (mixed)	211	12	92.5	6/5 1.19 (0.36, 3.97)	Adequate	2	No
Stroke (ischemic and/or hemorrhagic)											
Landray (2006) ¹⁶⁶ 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	1/0 7.70 (0.0.15, 388.20)	Adequate	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 statins, all doses, all clinical populations											
69 Rodney (2006) ¹¹¹ Pharm. Fund Multicentre	African descent, 1° HC	Simvastatin 20	124	Simvastatin 20	123	12	176	2/1 2.00 (0.18, 22.35)	Adequate	5	No
Barrios (2005) ¹¹² 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
Landray (2006) ¹⁶⁶ 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)	Adequate	2	Yes
Farnier (2005) ¹¹⁴ 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) ¹¹⁵ 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

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) ¹¹⁶ 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
Ballantyne (2005) ¹¹⁸ VYVA North America Pharm. Fund Multicenter	Participants with DM not at LDL-c ATP III goal off lipid lowering treatment	Simvastatin 10-80	220	Atorvastatin 10-80	206	6	178	3/6 0.46 (0.11, 1.87)	Adequate	2	No
Masana (2005) ¹⁶⁷ 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
Gaudiani (2005) ¹²¹ 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
Bays (2004) ¹⁵⁴ North America Pharm. Fund Multicentre	1° 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)	Adequate	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
Stein (2004) ¹⁵⁶ International Pharm. fund	Those with LDL \geq 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
Feldman (2004) ⁴⁷ 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
Goldberg (2004) ⁴⁸ Ezetimibe Study Group International Pharm. fund	1° 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)	Adequate	45	No
Ballantyne (2003) ¹²⁶ Ezetimibe Study Group International Pharm. Fund Multicentre	1° 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

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) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicentre	1° 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)	Adequate	4	No
Blagden (2007) ¹⁴⁰ 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
Ballantyne (2007) ¹⁴² Europe Pharm. Fund Multicentre	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	160190	5/4 0.78 (0.17, 3.53)	unclear	1	No
Patel (2006) ¹⁴³ 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) ¹⁴⁴ 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)	Adequate	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) ¹⁹³ North America Pharm. Fund Multicentre	Hypercholesterolemia, heterogeneous 10-year CHD risk estimates	Rosuvastatin/Simvastatin 20-80	1427	Rosuvastatin 10-40	1428	6	173	16/17 0.94 (0.47, 1.87)	Adequate	4	No
Shankar (2007) ¹⁶⁸ 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
Reckless (2008) ¹⁴⁹ INFORCE International Pharm. Fund Multicentre	CHD patients on previous stable statin dose	Simvastatin 40	213	Mixed statins	211	12	92.5	44/42 1.05 (0.65, 1.68)	Adequate	2	No
Roeters van Lennep (2008) ¹⁵¹ EASEGO Europe Pharm. Fund Multicentre	CHD and/or controlled type II DM patients not on target LDL-c despite prior low dose simvastatin or atorvastatin therapy	Simvastatin 20	178	Simvastatin 40 or atorvastatin 20	189	12	115	9/7 1.38 (0.50, 3.80)	Unclear	3	No
Gouni-Berthold (2008) ¹¹⁰ Europe Pharm. Fund Single	Healthy males with LDL-c < 190 mg/dL and < 60 years of age, previously not on lipid lowering treatment	Simvastatin 40	24	Simvastatin 40	24	2	114.5	0/0	Unclear	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
Conrad (2008) ¹⁵⁸ International Pharm. Fund Multicenter	Moderately high risk participants on atorvastatin 20 mg/day or statin naive and with LDL-c 100 mg/dL to ≤ 160 mg/dL	Atorvastatin 20	96	Atorvastatin 40	98	6	119	0/0	Adequate	5	No
Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c ≥ 130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	66	Simvastatin 40	34	4	169	3/0 3.80 (0.19, 75.78)	Adequate	5	Yes
Leiter (2008) ¹⁵⁹ North America Pharm. Fund Multicenter	Participants with or without prior lipid lowering therapy with 10-year CHD risk > 20%	Atorvastatin 40	286	Atorvastatin 80	289	6	89	9/5 1.85 (0.61, 5.58)	Adequate	5	No
Serious Adverse Events: all statins, lower versus higher doses, all clinical populations											
Gaudiani (2005) ¹²¹ 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
Feldman (2004) ⁴⁷ 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
Conrad (2008) ¹⁵⁸ International Pharm. Fund Multicenter	Moderately high risk participants on atorvastatin 20 mg/day or statin naive and with LDL-c 100 mg/dL to ≤ 160 mg/dL	Atorvastatin 20	96	Atorvastatin 40	98	6	119	0/0	Adequate	5	No
Dobs (2003) ¹⁶⁹ Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c ≥ 130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	66	Simvastatin 40	34	4	169	3/0 3.80 (0.19, 75.78)	Adequate	5	Yes
Cancer, all trials											
Goldberg (2004) ⁴⁸ Ezetimibe Study Group International Pharm. fund	1° 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)	Adequate	5	No
Landray (2006) ¹⁶⁶ 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)	Adequate	2	Yes

Table F-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 statins, all doses, all clinical populations											
Feldman (2004) ⁴⁷ 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) ¹⁵⁶ International Pharm. fund	1° 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) ¹²⁶ Ezetimibe Study Group International Pharm. Fund Multicenter	1° 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) ¹⁴⁸ International Pharm. fund	HC, Participants with documented statin associated muscle related side effects	Fluvastatin 80	64	Fluvastatin 80	69	12	174	54/41 3.69 (1.61, 8.44)	Adequate	5	yes
Kerzner (2003) ¹²⁹ Ezetimibe Study Group North America Pharm. Fund Multicenter	1° 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) ¹²⁷ Ezetimibe Study Group North America Pharm. Fund Multicenter	1° 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)	Adequate	4	yes
Davidson (2002) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° 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)	Adequate	4	no
Shankar (2007) ¹⁶⁸ 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) ¹¹² 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) ¹¹⁵ International Pharm. Fund Multicenter	Participants with CAD on low dose atorvastatins	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
Ballantyne (2005) ¹¹⁸ VYVA North America Pharm. Fund Multicenter	Participants not on ATP III target LDL-c (ATPIII criteria)	Simvastatin 10-80	923	Atorvastatin 10-80	927	6	178	828/752 2.03 (1.55, 2.65)	Adequate	2	no
Blagden (2007) ¹⁴⁰ 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) ¹⁴⁴ 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)	Adequate	3	no
Goldberg (2006_2) ¹⁴⁴ 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)	Adequate	3	no
Constance (2007) ¹⁹⁴ 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)	Adequate	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
Pearson (2005) ¹¹⁷ 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)	Adequate	4	no
Ballantyne (2007) ¹⁴² Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	190	221/182 4.16 (2.22, 7.79)	unclear	1	no
Catapano (2006) ¹⁹³ 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)	Adequate	3	no
Farnier (2005) ¹¹⁴ 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) ¹¹⁶ 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
Gaudiani (2005) ¹²¹ 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) ¹⁶⁷ Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals, DM subgroup	Simvastatin 10-80	73	Simvastatin 10-80	80	23	136	61/14 23.96 (10.28, 55.84)	unclear	3	no
Reckless (2008) ¹⁴⁹ INFORCE International Pharm. Fund Multicentre	CHD patients on previous stable statin dose	Simvastatin 40	197	Double the previous (mixed) statin dose	187	12	92.5	169/135 2.32 (1.39, 3.88)	Adequate	2	No
Roeters van Lennep (2008) ¹⁵¹ EASEGO Europe Pharm. Fund Multicentre	CHD and/or controlled type II DM patients not on target LDL-c despite prior low dose simvastatin or atorvastatin therapy	Simvastatin 20	178	Simvastatin 40 or atorvastatin 20	189	12	115	119/49 5.76 (3.67, 9.05)	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
Relative probability of attaining ATPIII LDL-c goal: all statins, lower versus higher doses, all clinical populations											
Feldman (2004) ⁴⁷ 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) ¹²¹ 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
Roeters van Lennep (2008) ¹⁵¹ EASEGO Europe Pharm. Fund Multicentre	CHD and/or controlled type II DM patients not on target LDL-c despite prior low dose simvastatin or atorvastatin therapy	Simvastatin 20	110	Simvastatin 40	115	12	115	80/28 8.29 (4.56, 15.07)	Unclear	3	Yes
Relative probability of attaining ATPIII LDL-c goal: all statins, all doses, intensive lipid lowering populations and clinical subgroups											
Ballantyne (2007) ¹⁴² Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	190	221/182 4.16 (2.22, 7.79)	unclear	1	no
Barrios (2005) ¹¹² 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

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) ¹⁴⁰ 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) ¹¹⁶ 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
Pearson (2005) ¹¹⁷ 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)	Adequate	4	no
Constance (2007) ¹⁹⁴ 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)	Adequate	3	no
Cruz-Fernandez (2005) ¹¹⁵ 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) ¹¹⁴ 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

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) ⁴⁷ 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
Gaudiani (2005) ¹²¹ 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) ¹⁴⁴ 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)	Adequate	3	no
Goldberg (2006_2) ¹⁴⁴ 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)	Adequate	3	no
Stein (2008) ¹⁴⁸ International Pharm. fund	HC, Participants with documented statin associated muscle related side effects	Fluvastatin 80	30	Fluvastatin 80	33	12	174	24/14 5.43 (1.75, 16.80)	Adequate	5	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
Masana (2005) ¹⁶⁷ Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals, DM subgroup	Simvastatin 10-80	73	Simvastatin 10-80	80	23	136	61/14 23.96 (10.28, 55.84)	unclear	3	no
Shankar (2007) ¹⁶⁸ 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
Catapno (2006) ¹⁹³ North America Pharm. Fund Multicenter	Participants with DM	Simvastatin 20-80	186	Rosuvastatin 20-40	181	6	173	170/161 1.32 (0.66, 2.64)	Adequate	3	No
Reckless (2008) ¹⁴⁹ INFORCE International Pharm. Fund Multicentre	CHD patients on previous stable statin dose	Simvastatin 40	197	Double the previous (mixed) statin dose	187	12	92.5	169/135 2.32 (1.39, 3.88)	Adequate	2	No
Roeters van Lennep (2008) ¹⁵¹ EASEGO Europe Pharm. Fund Multicentre	CHD and/or controlled type II DM patients not on target LDL-c despite prior low dose simvastatin or atorvastatin therapy	Simvastatin 20	178	Simvastatin 40 or atorvastatin 20	189	12	115	119/49 5.76 (3.67, 9.05)	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
Ballantyne (2005) ¹¹⁸ VYVA North America Pharm. Fund Multicenter	Participants with DM not at LDL-c ATP III goal off lipid lowering treatment	Simvastatin 10-80	212	Atorvastatin 10-80	201	6	178	170/161 2.94 (1.70, 5.06)	Adequate	2	no
Reckless (2008) ¹⁴⁹ INFORCE International Pharm. Fund Multicentre	Participants with diabetes mellitus	Simvastatin 40	57	Double the previous (mixed) statin dose	51	12	92.5	49/39 1.88 (0.70, 5.06)	Adequate	2	No
Reckless (2008) ¹⁴⁹ INFORCE International Pharm. Fund Multicentre	Female participants only	Simvastatin 40	40	Double the previous (mixed) statin dose	36	12	92.5	31/21 2.46 (0.91, 6.65)	Adequate	2	No
Farnier (2005) ¹¹⁴ International Pharm. Fund Multicentre	Female participants only	Simvastatin 10-20	56	Simvastatin 10-20	57	6	123	43/9 17.64 (6.86, 45.36)	Unclear	5	No
Pearson (2005) ¹¹⁷ EASE North America Pharm. Fund Multicenter	Participants of African descent not meeting ATP III target LDL-c despite statin therapy	Mixed	135	Mixed	73	6	129	85/24 3.47 (1.90, 6.33)	Adequate	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
Pearson (2005) ¹¹⁷ EASE North America Pharm. Fund Multicenter	Hispanic 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)	Adequate	4	no
Relative probability of attaining ATPIII LDL-c goal: all statins, lower versus higher doses, intensive lipid lowering populations and clinical subgroups											
Feldman (2004) ⁴⁷ 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) ¹²¹ 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
Roeters van Lennep (2008) ¹⁵¹ EASEGO Europe Pharm. Fund Multicentre	CHD and/or controlled type II DM patients not on target LDL-c despite prior low dose simvastatin or atorvastatin therapy	Simvastatin 20	110	Simvastatin 40	115	12	115	80/28 8.29 (4.56, 15.07)	Unclear	3	Yes

Table F-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 mean percentage change from baseline (%): all statins, all doses, all clinical populations											
Kastelein (2008) ⁴² ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	-16.50 (-16.63, -16.37)	Adequate	3	no
Ballantyne (2003) ¹²⁶ Ezetimibe Study Group International Pharm. Fund Multicenter	1° 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) ⁴⁶ 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) ¹⁶⁶ 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)	Adequate	2	no

Gaudiani (2005) ¹²¹ 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) ¹⁵⁴ North America Pharm. Fund Multicenter	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	539	Simvastatin 10-80	559	6-26	178	-14.90 (-16.46, -13.34)	Adequate	5	no
Berthold (2006) ¹⁰⁹ 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) ¹⁵⁶ 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) ¹¹¹ Pharm. Fund Multicenter	African descent, 1° HC	Simvastatin 20	124	Simvastatin 20	123	12	176	-17.20 (-21.13, -13.27)	Adequate	5	no
Masana (2005) ¹⁶⁷ 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) ⁴⁸ Ezetimibe Study Group International Pharm. fund	statin naïve, 1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	323	Simvastatin 10-80	322	12	175	-14.70 (-17.13, -12.27)	Adequate	5	no

Melani (2003) ¹²⁷ 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	-13.40 (-15.89, - 10.91)	Adequate	4	yes
Kerzner (2003) ¹²⁹ Ezetimibe Study Group North America Pharm. Fund Multicenter	1° 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) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 10-80	253	Simvastatin 10-80	249	12	179	-15.20 (-17.70, - 12.70)	Adequate	4	no
Gagne (2002_1) ¹³² 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) ¹³² 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) ¹³⁹ 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) ¹⁶⁸ 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) ¹⁶⁷ Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals, subgroup with DM	Mixed 10-80	88	Mixed 10-80	94	8	136	-26.10 (-30.69, -21.51)	unclear	3	no
Barrios (2005) ¹¹² 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) ¹¹⁴ 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) ¹¹⁵ 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) ¹¹⁶ 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) ¹¹⁷ 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)	Adequate	4	no

Pearson (2005) ¹¹⁷ 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)	Adequate	4	no
Pearson (2005) ¹¹⁷ 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)	Adequate	4	no
Ballantyne (2005_1) ¹¹⁸ 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)	Adequate	2	no
Ballantyne (2005_2) ¹¹⁸ 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)	Adequate	2	no
Ballantyne (2005_3) ¹¹⁸ 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)	Adequate	2	no
Blagden (2007) ¹⁴⁰ 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) ¹⁴² Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	190	-24.60 (-29.39, -19.81)	unclear	1	no
Patel (2006) ¹⁴³ 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) ¹⁴⁴ 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)	Adequate	3	no
Goldberg (2006_2) ¹⁴⁴ 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)	Adequate	3	no
Catapano (2006) ¹⁹³ 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)	Adequate	3	no
Constance (2007) ¹⁹⁴ International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20	210	Atorvastatin 20	213	6	94	-17.66 (-22.78, -12.54)	Adequate	3	no
Feldman (2004) ⁴⁷ North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 40	97	Simvastatin 40	248	23	169	-14.00 (-17.53, -10.47)	unclear	2	no
Kosoglou (2004) ¹²⁴ Europe Pharm. Fund Single centre	Healthy participants with LDL-c ≥ 130 mg/dL and BMI < 31kg/m2. Low risk	Rosuvastatin 10	12	Rosuvastatin 10	11	2	158	-15.90 (-22.16, -9.64)	unclear	2	yes

Gouni-Berthold (2008) ¹¹⁰ Europe Pharm. Fund Single	Healthy males with LDL-c < 190 mg/dL and < 60 years of age, previously not on lipid lowering treatment	Simvastatin 40	24	Simvastatin 40	24	2	114.5	-18.90 (-24.97, -12.83)	Unclear	2	Yes
Conrad (2008) ¹⁵⁸ International Pharm. Fund Multicenter	Moderately high risk participants on atorvastatin 20 mg/day or statin naive and with LDL-c 100 mg/dL to ≤ 160 mg/dL	Atorvastatin 20	92	Atorvastatin 40	92	6	119	-19.90 (-25.17, -14.63)	Adequate	5	No
Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c ≥ 130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	66	Simvastatin 40	34	4	169	-13.36 (-18.31, -8.41)	Adequate	5	Yes
Leiter (2008) ¹⁵⁹ North America Pharm. Fund Multicenter	Participants with or without prior lipid lowering therapy with 10-year CHD risk > 20%	Atorvastatin 40	277	Atorvastatin 80	279	6	89	-16.40 (-19.45, -13.35)	Adequate	5	No
Combination – monotherapy, difference in mean percentage change from baseline (%):all statins, lower versus higher doses, all clinical populations											
Gaudiani (2005) ¹²¹ 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_1) ¹⁵⁴ North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 10	222	Simvastatin 40	108	6-26	178	-5.90 (-8.80, -3.00)	Adequate	5	no
Bays (2004_2) ¹⁵⁴ North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 20	106	Simvastatin 80	224	6-26	178	-3.00 (-5.93, -0.07)	Adequate	5	no
Feldman (2004) ⁴⁷ North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 20	109	Simvastatin 40	248	23	169	-10.00 (-13.19, -6.81)	unclear	2	no
Goldberg (2004_1) ⁴⁸ Ezetimibe Study Group International Pharm. fund	statin naïve, 1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 10	87	Simvastatin 40	90	12	175	-4.70 (-8.19, -0.49)	Adequate	5	no
Goldberg (2004_2) ⁴⁸ Ezetimibe Study Group International Pharm. fund	statin naïve, 1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 20	86	Simvastatin 80	87	12	175	-4.90 (-9.21, -0.59)	Adequate	5	no
Davidson (2002_1) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 10	67	Simvastatin 40	64	12	179	-8.12 (-13.03, -3.21)	Adequate	4	no

Davidson (2002_2) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 20	68	Simvastatin 80	66	12	179	-0.53 (-5.39, -4.33)	Adequate	4	no
Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c >=130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	66	Simvastatin 40	34	4	169	-13.36 (-18.31, -8.41)	Adequate	5	Yes
Combination – monotherapy, difference in mean percentage change from baseline (%):all statins, all doses, intensive lipid lowering populations and clinical subgroups											
Barrios (2005) ¹¹² 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) ¹¹⁴ 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) ¹¹⁵ 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) ¹¹⁶ 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) ¹⁶⁷ Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals, subgroup with DM	Mixed 10-80	88	Mixed 10-80	94	8	136	-26.10 (-30.69, -21.51)	unclear	3	no
Gaudiani (2005) ¹²¹ 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) ⁴⁷ North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 40	186	Simvastatin 40	181	23	169	-14.00 (-17.53, -10.47)	unclear	2	no
Gagne (2002_2) ¹³² 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) ¹⁴⁰ 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) ¹⁴² Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	190	-24.60 (-29.39, -19.81)	unclear	1	no
Patel (2006) ¹⁴³ 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) ¹⁴⁴ 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)	Adequate	3	no
Constance (2007) ¹⁹⁴ International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20	210	Atorvastatin 20	213	6	94	-17.66 (-22.78, -12.54)	Adequate	3	no
Kastelein (2008) ⁴² ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	-16.50 (-16.63, -16.37)	Adequate	3	no
Ballantyne (2005) ¹¹⁸ VYVA North America Pharm. Fund Multicenter	Participants with DM not at LDL-c ATP III goal off lipid lowering treatment	Simvastatin 10-80	212	Atorvastatin 10-80	201	6	178	-10.20 (-13.25, -7.15)	Adequate	2	no
Bays (2004) ¹⁵⁴ North America Pharm. Fund Multicentre	Mixed 10 years CHD risk participants who were protocol compliant in a previous base study	Simvastatin 10-80	86	Simvastatin 10-80	69	6-26	178	-9.40 (-13.62, -5.18)	Adequate	5	No
Catapno (2006) ¹⁹³ North America Pharm. Fund Multicenter	Participants with DM	Simvastatin 20-80	186	Rosuvastatin 10-40	181	6	173	-4.30 (-6.79, -1.81)	Adequate	3	No
Leiter (2008) ¹⁵⁹ North America Pharm. Fund Multicenter	Participants with or without prior lipid lowering therapy with 10-year CHD risk > 20%	Atorvastatin 40	277	Atorvastatin 80	279	6	89	-16.40 (-19.45, -13.35)	Adequate	5	No

Bays (2004) ¹⁵⁴ North America Pharm. Fund Multicentre	Participants with DM	Simvastatin 10-80	34	Simvastatin 10-80	37	6-26	178	-14.40 (-21.18, -7.62)	Adequate	5	No
Rodney (2006) ¹¹¹ Pharm. Fund Multicentre	African descent, 1° HC	Simvastatin 20	124	Simvastatin 20	124	12	176	-17.2 (-21.1, - 13.27)	Adequate	5	No
Farnier (2005) ¹¹⁴ International Pharm. Fund Multicentre	Participants with CAD on low dose simvastatin -- African descent	Simvastatin 10-20	1	Simvastatin 10-20	1	6	111	NA	unclear	5	No
Pearson (2005) ¹¹⁷ EASE North America Pharm. Fund Multicentre	Participants not meeting ATP III target LDL-c despite statin therapy -- African descent	Mixed	174	Mixed	93	6	129	-23 (-27.5, - 18.45)	Adequate	4	No
Bays (2004) ¹⁵⁴ North America Pharm. Fund Multicentre	Participants with CHD	Simvastatin 10-80	34	Simvastatin 10-80	37	6-26	180	-9.40 (-13.62, - 5.18)	Adequate	5	No
Farnier (2005) ¹¹⁴ International Pharm. Fund Multicentre	Participants with CAD on low dose simvastatin -- Females only	Simvastatin 10-20	56	Simvastatin 10-20	57	6	111	-23.99 (-30.53, -17.45)	unclear	5	No
Davidson (2002) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates -- Females only	Simvastatin 10-80	152	Simvastatin 10-80	147	12	179	13.4 (9.87, 16.93)	Adequate	4	no

Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates, with (LDL-c >=130 mg/dL) not controlled on simvastatin 20 mg/day -- Females only,	Simvastatin 20	29	Simvastatin 40	15	4	169	-14.46 (-21.90, -7.02)	Adequate	5	Yes
Pearson (2005) ¹¹⁷ 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)	Adequate	4	no
Gagne (2002_1) ¹³² Ezetimibe Study Group International Pharm. fund	Homozygous FHC, 7 (14%) participants between 12-18 years of age – LDL > 190	Atorvastatin 80	12	Atorvastatin 80	12	12	309	-21.16 (-30.97, - 11.35)	unclear	3	no
Gagne (2002_2) ¹³² Ezetimibe Study Group International Pharm. fund	Homozygous FHC, 7 (14%) participants between 12-18 years of age, LDL > 190	Simvastatin 80	5	Simvastatin 80	5	12	309	-18.83 (-36.43, -1.23)	unclear	3	no
Kastelein (2008) ⁴² ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	-16.50 (-16.63, - 16.37)	Adequate	3	no

Combination – monotherapy, difference in mean percentage change from baseline (%):all statins, lower versus higher doses, intensive lipid lowering populations and clinical subgroups											
Gaudiani (2005) ¹²¹ 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_1) ¹⁵⁴ North America Pharm. Fund Multicenter	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	222	Simvastatin 40	108	6-26	178	-5.90 (-8.80, -3.00)	Adequate	5	no
Bays (2004_2) ¹⁵⁴ North America Pharm. Fund Multicenter	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	106	Simvastatin 80	224	6-26	178	-3.00 (-5.93, -0.07)	Adequate	5	no
Feldman (2004) ⁴⁷ North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 20	109	Simvastatin 40	248	23	169	-10.00 (-13.19, -6.81)	unclear	2	no
Goldberg (2004_1) ⁴⁸ Ezetimibe Study Group International Pharm. fund	statin naïve, 1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	87	Simvastatin 40	90	12	175	-4.70 (-8.19, -0.49)	Adequate	5	no
Goldberg (2004_2) ⁴⁸ Ezetimibe Study Group International Pharm. fund	statin naïve, 1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	86	Simvastatin 80	87	12	175	-4.90 (-9.21, -0.59)	Adequate	5	no

Davidson (2002_1) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	67	Simvastatin 40	64	12	179	-8.12 (-13.03, -3.21)	Adequate	4	no
Davidson (2002_2) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	68	Simvastatin 80	66	12	179	-0.53 (-5.39, -4.33)	Adequate	4	no
Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c >=130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	66	Simvastatin 40	34	4	169	-13.36 (-18.31, -8.41)	Adequate	5	Yes
Davidson (2002_1) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10-year CHD risk estimates -- Females only	Simvastatin 10	36	Simvastatin 40	35	12	179	-9.80 (-16.05, -3.55)	Adequate	4	no
Davidson (2002_2) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10-year CHD risk estimates -- Females only	Simvastatin 20	34	Simvastatin 80	37	12	179	-1.8 (9.70, 6.10)	Adequate	4	no

Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates, with (LDL-c ≥130 mg/dL) not controlled on simvastatin 20 mg/day -- Females only,	Simvastatin 20	29	Simvastatin 40	15	4	169	-14.46 (-21.90, -7.02)	Adequate	5	Yes
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Table F-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 mean percentage change from baseline (%):all statins, all doses, all clinical populations											
Kastelein (2008) ⁴² ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	357	Simvastatin 80	363	96	318	2.40 (-0.23, 5.03)	Adequate	3	No
Ballantyne (2003) ¹²⁶ Ezetimibe Study Group International Pharm. Fund Multicenter	1° 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) ⁴⁶ 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) ¹⁵⁶ International Pharm. Fund	1° 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) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	253	Simvastatin 10-80	249	12	179	2.40 (0.18, 4.62)	Adequate	4	No

Goldberg (2004) ⁴⁸ Ezetimibe Study Group International Pharm. fund	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	323	Simvastatin 10-80	322	12	175	0.60 (-1.33, 2.53)	Adequate	5	No
Kerzner (2003) ¹²⁹ Ezetimibe Study Group North America Pharm. Fund Multicenter	1° 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) ¹⁶⁷ 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) ¹³⁹ 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) ¹²⁷ 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	1.40 (-0.82, 3.62)	Adequate	4	Yes
Shankar (2007) ¹⁶⁸ 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) ¹⁴² Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	190	2.32 (-0.83, 5.47)	unclear	1	No
Barrios (2005) ¹¹² 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) ¹⁴⁰ 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) ¹¹⁶ 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) ¹⁹³ 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)	Adequate	3	No
Constance (2007) ¹⁹⁴ 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)	Adequate	3	No
Cruz-Fernandez (2005) ¹¹⁵ 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) ¹²¹ North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinedione s, 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) ⁴⁷ 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) ¹⁵⁴ North America Pharm. Fund Multicenter	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	539	Simvastatin 10-80	559	6-26	178	0.80 (-0.72, 2.32)	Adequate	5	No
Berthold (2006) ¹⁰⁹ 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) ¹²⁴ Europe Pharm. Fund Single centre	Healthy participants with LDL-c ≥ 130 mg/dL and BMI < 31kg/m ² . Low risk	Rosuvastatin 10	12	Rosuvastatin 10	11	2	158	-2.80 (-11.57, 5.97)	unclear	2	Yes
Landray (2006) ¹⁶⁶ 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)	Adequate	2	Yes

Pearson (2005) ¹¹⁷ 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)	Adequate	4	No
Gouni-Berthold (2008) ¹¹⁰ Europe Pharm. Fund Single	Healthy males with LDL-c < 190 mg/dL and < 60 years of age, previously not on lipid lowering treatment	Simvastatin 40	24	Simvastatin 40	24	2	114.5	-2.20 (-7.79, 3.39)	Unclear	2	Yes
Conrad (2008) ¹⁵⁸ International Pharm. Fund Multicenter	Moderately high risk participants on atorvastatin 20 mg/day or statin naive and with LDL-c 100 mg/dL to ≤ 160 mg/dL	Atorvastatin 20	92	Atorvastatin 40	92	6	119	2.40 (1.97, 2.83)	Adequate	5	No
Leiter (2008) ¹⁵⁹ North America Pharm. Fund Multicenter	Participants with or without prior lipid lowering therapy with 10-year CHD risk > 20%	Atorvastatin 40	277	Atorvastatin 80	279	6	89	0.50 (-1.16, 2.16)	Adequate	5	No
Ballantyne (2005) ¹¹⁸ VYVA North America Pharm. Fund Multicenter	Participants with DM not at LDL-c ATP III goal off lipid lowering treatment	Simvastatin 10-80	212	Atorvastatin 10-80	201	6	178	2.60 (0.10, 5.10)	Adequate	2	no
Goldberg (2006_1) ¹⁴⁴ VYTAL North America Pharm. Fund Multicenter	Participants with type II DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dl	Simvastatin 20	240	Atorvastatin 20	238	6	145	3.50 1.28, 5.72)	Adequate	3	No

Goldberg (2006_2) ¹⁴⁴ VYTAL North America Pharm. Fund Multicenter	Participants with type II DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dl	Simvastatin 40	241	Atorvastatin 40	242	6	145	4.00 1.78, 6.22)	Adequate	3	No
Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c >=130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 30	66	Simvastatin 40	34	4	169	1.23 (-2.43, 4.89)	Adequate	5	Yes
Farnier (2005) ¹¹⁴ International Pharm. Fund Multicentre	Participants with CAD on low dose simvastatin	Simvastatin 10-20	179	Simvastatin 10-20	186	6	123	0.75 (-2.01, 3.51)	Unclear	5	No
Combination – monotherapy, difference in mean percentage change from baseline (%):all statins, lower versus higher doses, all clinical populations											
Barrios (2005) ¹¹² 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) ¹¹⁵ 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) ¹¹⁶ 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) ¹¹⁷ 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)	Adequate	4	No
Masana (2005) ¹⁶⁷ Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals, DM subgroup	Mixed 10-80	88	Mixed 10-80	94	12	136	-0.80 (0.43, 2.09)	unclear	3	No
Gaudiani (2005) ¹²¹ North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinedione s, 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) ⁴⁷ 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) ¹⁴⁰ 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) ¹⁴² Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	190	2.32 (-0.83, 5.47)	unclear	1	No

Constance (2007) ¹⁹⁴ 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)	Adequate	3	No
Kastelein (2008) ⁴² 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)	Adequate	3	No
Farnier (2005) ¹¹⁴ International Pharm. Fund Multicentre	Participants with CAD on low dose simvastatin	Simvastatin 10-20	179	Simvastatin 10-20	186	6	123	0.75 (-2.01, 3.51)	Unclear	5	No
Ballantyne (2005) ¹¹⁸ VYVA North America Pharm. Fund Multicenter	Participants with DM not at LDL-c ATP III goal off lipid lowering treatment	Simvastatin 10-80	212	Atorvastatin 10-80	201	6	178	2.6 (0.10, 5.10)	Adequate	2	no
Goldberg (2006_1) ¹⁴⁴ VYTAL North America Pharm. Fund Multicenter	Participants with type II DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dl – entered into diabetes subgroup analysis	Simvastatin 20	238	Atorvastatin 20	240	6	145	3.50 (1.28, 5.72)	Adequate	3	No

Goldberg (2006_2) ¹⁴⁴ VYTAL North America Pharm. Fund Multicenter	Participants with type II DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dl – entered into diabetes subgroup analysis	Simvastatin 40	242	Atorvatstatin 40	241	6	145	4.00 (1.78, 6.22)	Adequate	3	No
Catapno (2006) ¹⁹³ North America Pharm. Fund Multicenter	Participants with DM	Simvastatin 20-80	186	Rosuvastatin 10-40	181	6	173	0.7 (-1.52, 2.92)	Adequate	3	No
Leiter (2008) ¹⁵⁹ North America Pharm. Fund Multicenter	Participants with or without prior lipid lowering therapy with 10- year CHD risk > 20%	Atorvatstatin 40	277	Atorvatstatin 80	279	6	89	0.5 (-1.16, 2.16)	Adequate	5	No
Pearson (2005) ¹¹⁷ 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	3.30 (0.35, 6.25)	Adequate	4	No
Pearson (2005) ¹¹⁷ 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	0.30 (-3.64, 4.24)	Adequate	4	No

Combination – monotherapy, difference in mean percentage change from baseline (%):all statins, lower versus higher doses, intensive lipid lowering populations and clinical subgroups											
Gaudiani (2005) ¹²¹ North America Pharm. Fund Multicenter	Participants with T2DM on stable thiazolidinedione s, 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

Table F-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 mean percentage change from baseline: all statins, all doses, all clinical populations											
Masana (2005) ¹⁶⁷ 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) ⁴⁸ Ezetimibe Study Group International Pharm. fund	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	323	Simvastatin 10-80	322	12	175	-10.90 (-13.01, -8.79)	Adequate	5	no
Ballantyne (2003) ¹²⁶ Ezetimibe Study Group International Pharm. Fund Multicenter	1° 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) ¹²⁷ 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	-13.10 (-15.59, - 10.61)	Adequate	4	yes

Kerzner (2003) ¹²⁹ Ezetimibe Study Group North America Pharm. Fund Multicenter	1° 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) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10-80	253	Simvastatin 10-80	249	12	179	-11.16 (-13.38, -8.94)	Adequate	4	no
McKenney (2007_1) ¹³⁹ COMPELL study North America Pharm. Fund Multicenter	HC, heterogeneous 10-year CHD risk estimates	Simvastatin 40	72	Rosuvastatin 40	73	12	197	-4.00 (-7.91, -0.09)	unclear	2	no
Barrios (2005) ¹¹² 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) ¹¹⁵ 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) ¹²¹ 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) ¹⁴² Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	190	-10.36 (-12.62, -8.10)	unclear	4	no
Constance (2007) ¹⁹⁴ 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)	Adequate	3	no
Catapano (2006) ¹⁹³ North America Pharm. Fund Multicenter	Hypercholesterol emia, heterogeneous 10-year CHD risk estimates	Simvastatin 20-80	1427	Rosuvastatin 10-40	1428	6	173	-3.00 (-3.83, -2.17)	Adequate	4	no
Bays (2007) ¹⁵⁴ North America Pharm. Fund Multicenter	1° HC	Simvastatin 10-80	539	Simvastatin 10-80	559	6-26	178	-10.50 (-11.95, -9.05)	Adequate	3	no
Stein (2004) ¹⁵⁶ International Pharm. fund	1° HC, LDL ≥ 130 mg/dL despite diet and atorvastatin 10 mg/day	Atorvastatin 40	278	Atorvastatin 80	290	14	186	-17.00 (-18.95, -15.05)	unclear	3	yes

Conrad (2008) ¹⁵⁸ International Pharm. Fund Multicenter	Moderately high risk participants on atorvastatin 20 mg/day or statin naive and with LDL-c 100 mg/dL to ≤ 160 mg/dL	Atorvastatin 20	92	Atorvastatin 40	92	6	119	-13.00 (-17.61, -8.39)	Adequate	5	No
Leiter (2008) ¹⁵⁹ North America Pharm. Fund Multicenter	Participants with or without prior lipid lowering therapy with 10-year CHD risk > 20%	Atorvastatin 40	277	Atorvastatin 80	279	6	89	-10.40 (-12.62, -8.18)	Adequate	5	No
Ballantyne (2005) ¹¹⁸ VYVA North America Pharm. Fund Multicenter	Participants with DM not at LDL-c ATP III goal off lipid lowering treatment	Simvastatin 10-80	212	Atorvastatin 10-80	201	6	178	-7.50 (-9.85, -5.15)	Adequate	2	no
Goldberg (2006_a) ¹⁴⁴ VYTAL North America Pharm. Fund Multicenter	Participants with type II DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dl	Simvastatin 20	240	Atorvastatin 20	241	6	145	3.00 (0.78, 5.22)	Adequate	3	No
Goldberg (2006_b) ¹⁴⁴ VYTAL North America Pharm. Fund Multicenter	Participants with type II DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dl	Simvastatin 40	238	Atorvastatin 40	242	6	145	1.90 (-0.32, 4.12)	Adequate	3	No

Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c \geq 130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	66	Simvastatin 40	34	4	169	-9.88 (-14.64, -5.12)	Adequate	5	Yes
Combination – monotherapy, difference in mean percentage change from baseline: all statins, lower versus higher doses, all clinical populations											
Conrad (2008) ¹⁵⁸ International Pharm. Fund Multicenter	Moderately high risk participants on atorvastatin 20 mg/day or statin naive and with LDL-c 100 mg/dL to \leq 160 mg/dL	Atorvastatin 20	92	Atorvastatin 40	92	6	119	-13.00 (-17.61, -8.39)	Adequate	5	No
Gaudiani (2005) ¹²¹ 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
Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c \geq 130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	66	Simvastatin 40	34	4	169	-9.88 (-14.64, -5.12)	Adequate	5	Yes

Bays (2004_1) ¹⁵⁴ North America Pharm. Fund Multicentre	Mixed 10 years CHD risk participants who were protocol compliant in a previous base study	Simvastatin 10	222	Simvastatin 40	108	6-26	178	-3.70 (-6.38, -1.02)	Adequate	5	No
Bays (2004_2) ¹⁵⁴ North America Pharm. Fund Multicentre	Mixed 10 years CHD risk participants who were protocol compliant in a previous base study	Simvastatin 20	106	Simvastatin 80	224	6-26	178	-1.40 (-4.12, 1.32)	Adequate	5	No
Goldberg (2004_1) ⁴⁸ Ezetimibe Study Group International Pharm. fund	Statin naïve, 1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 10	87	Simvastatin 40	90	12	175	-3.30 (-7.22, 0.62)	Adequate	5	No
Goldberg (2004_2) ⁴⁸ Ezetimibe Study Group International Pharm. fund	Statin naïve, 1° HC, heterogeneous 10-year CHD risk estimates	Simvastatin 20	86	Simvastatin 80	87	12	175	-3.10 (-7.06, 0.86)	Adequate	5	No
Davidson (2002_1) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicentre	Mixed 10 years CHD risk	Simvastatin 10	67	Simvastatin 40	64	12	179	-6.82 (- 11.23, -2.41)	Adequate	4	No

Davidson (2002_2) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicentre	Mixed 10 years CHD risk	Simvastatin 20	68	Simvastatin 80	66	12	179	-1.01 (-5.38, 3.36)	Adequate	4	No
Combination – monotherapy, difference in mean percentage change from baseline: all statins, all doses, intensive lipid lowering populations and clinical subgroups											
Barrios (2005) ¹¹² 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) ¹¹⁵ 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) ¹⁶⁷ Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals, DM subgroup	Mixed 10-80	88	Mixed 10-80	94	8	136	-17.30 (-20.91, - 13.69)	unclear	3	no
Gaudiani (2005) ¹²¹ 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) ¹⁴² Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	235	Rosuvastatin 40	230	6	190	-10.36 (-12.62, - 8.10)	unclear	4	no

Constance (2007) ¹⁹⁴ 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)	Adequate	3	no
Leiter (2008) ¹⁵⁹ North America Pharm. Fund Multicenter	Participants with or without prior lipid lowering therapy with 10-year CHD risk > 20%	Atorvastatin 40	277	Atorvastatin 80	279	6	89	-10.40 (-12.62, -8.18)	Adequate	5	No
Ballantyne (2005) ¹¹⁸ VYVA North America Pharm. Fund Multicenter	Participants with DM not at LDL-c ATP III goal off lipid lowering treatment	Simvastatin 10-80	212	Atorvastatin 10-80	201	6	178	-7.50 (-9.85, -5.15)	Adequate	2	no
Catapno (2006) ¹⁹³ North America Pharm. Fund Multicenter	Participants with DM	Simvastatin 20-80	186	Rosuvastatin 10-40	181	6	173	-3.40 (-5.34, -1.46)	Adequate	3	No
Goldberg (2006_1) ¹⁴⁴ VYTAL North America Pharm. Fund Multicenter	Participants with type II DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dl	Simvastatin 20	238	Atorvastatin 20	240	6	145	-6.70 (-8.92, -4.48)	Adequate	3	No
Goldberg (2006_2) ¹⁴⁴ VYTAL North America Pharm. Fund Multicenter	Participants with type II DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dl	Simvastatin 40	242	Atorvastatin 40	241	6	145	-5.60 (-7.82, -3.38)	Adequate	3	No

Combination – monotherapy, difference in mean percentage change from baseline: all statins, lower versus higher doses, intensive lipid lowering populations and clinical subgroups											
Gaudiani (2005) ¹²¹ 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

Table F-6 Surrogate outcome – Non-HDL-c using ezetimibe plus statin therapy compared with statin monotherapy in participants with diabetes mellitus

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 mean percentage change from baseline											
Masana (2005) ¹⁶⁷ Ezetimibe study group International Pharm. fund	Participants on stable statin treatment but not on ATP II LDL-c goals, DM subgroup	Mixed 10-80	88	Mixed 10-80	94	8	136	-23.80 (-27.96, -19.64)	unclear	3	no
Gaudiani (2005) ¹²¹ 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	-18.30 (-23.98, -12.62)	unclear	3	no
Ballantyne (2005) ¹¹⁸ VYVA North America Pharm. Fund Multicenter	Participants with DM not at LDL-c ATP III goal off lipid lowering treatment	Simvastatin 10-80	212	Atorvastatin 10-80	201	6	178	-8.30 (-11.07, -5.53)	Adequate	2	no
Catapno (2006) ¹⁹³ North America Pharm. Fund Multicenter	Participants with DM	Simvastatin 20-80	186	Rosuvastatin 10-40	181	6	173	-4.20 (-6.42, -1.98)	Adequate	3	No

Goldberg (2006_1) ¹⁴⁴ VYTAL North America Pharm. Fund Multicenter	Participants with type II DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dl	Simvastatin 20	238	Atorvatstatin 20	240	6	145	-6.70 (-8.92, - 4.48)	Adequate	3	No
Goldberg (2006_2) ¹⁴⁴ VYTAL North America Pharm. Fund Multicenter	Participants with type II DM, hemoglobin A-1c < 8.5% and LDL-c > 100 mg/dl	Simvastatin 40	242	Atorvatstatin 40	241	6	145	-5.60 (-7.82, - 3.38)	Adequate	3	No
Constance (2007) ¹⁹⁴ International Pharm. fund	Participants with T2DM on low dose atorvastatin	Simvastatin 20-40	439	Atorvastatin 20	218	6	94	-14.92 (-19.53, -10.31)	Adequate	3	No

Table F-7. Carotid intima-media thickness (CMT) 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) ⁴² ENHANCE International Pharm. fund	FHC, LDL-c > 210 mg/dL	Simvastatin 80	322	Simvastatin 80	320	96	318	0.01 (-0.01, 0.02)	Adequate	3	No

Table F-8. 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: all statins, all doses, all clinical populations											
Kastelein (2008) ⁴² 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)	Adequate	3	no
Landray (2006) ¹⁶⁶ 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)	Adequate	2	yes
Ballantyne (2004_b) ⁴⁶ 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) ¹⁵⁶ International Pharm. fund	1° 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) ⁴⁸ Ezetimibe Study Group International Pharm. fund	1° 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)	Adequate	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) ¹²⁷ 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	184/192 0.62 (0.30, 1.29)	Adequate	4	yes
Davidson (2002_1) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 10	67	Simvastatin 10	70	12	179	61/61 1.50 (0.50, 4.47)	Adequate	4	no
Davidson (2002_2) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 20	69	Simvastatin 20	61	12	179	58/53 0.80 (0.30, 2.13)	Adequate	4	no
Davidson (2002_3) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 40	73	Simvastatin 40	65	12	179	68/60 1.13 (0.31, 4.11)	Adequate	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) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 80	65	Simvastatin 80	67	12	179	52/63 0.25 (0.08, 0.83)	Adequate	4	no
McKenney (2007_1) ¹³⁹ 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) ¹¹⁵ 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) ¹⁴² Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	239	Rosuvastatin 40	230	6	190	232/219 1.66 (0.63, 4.37)	unclear	1	no
Patel (2006) ¹⁴³ 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

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
Reckless (2008) ¹⁴⁹ INFORCE International Pharm. Fund Multicentre	CHD patients on previous stable statin dose	Simvastatin 40	207	Double the previous (mixed) statin dose	213	12	92.5	207/205 1.01 (0.32, 3.18)	Adequate	2	No
Relative probability of participants adhering to treatment - all statins, lower versus higher doses, all clinical populations											
Davidson (2002_5) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 10	67	Simvastatin 40	65	12	179	61/60 0.85 (0.25, 2.93)	Adequate	4	no
Davidson (2002_6) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 20	69	Simvastatin 80	67	12	179	58/63 0.33 (0.10, 1.11)	Adequate	4	no
Relative probability of participants experiencing an adverse event: all statins, all doses, all clinical populations											
Ballantyne (2003) ¹²⁶ Ezetimibe Study Group International Pharm. Fund Multicenter	1° 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

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) ¹⁶⁷ 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
Goldberg (2004) ⁴⁸ 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)	Adequate	5	no
Ballantyne (2004_b) ⁴⁶ 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) ⁴⁷ 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) ¹⁵⁴ 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)	Adequate	5	no
Stein (2004) ¹⁵⁶ 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

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) ¹¹¹ Pharm. Fund Multicenter	African descent, 1° HC	Simvastatin 20	124	Simvastatin 20	123	12	176	71/69 1.05 (0.63, 1.73)	Adequate	5	no
Melani (2003) ¹²⁷ 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	134/129 1.13 (0.75, 1.69)	Adequate	4	yes
Kerzner (2003) ¹²⁹ Ezetimibe Study Group North America Pharm. Fund Multicenter	1° 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) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° 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)	Adequate	4	no
Shankar (2007) ¹⁶⁸ 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) ¹¹² 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) ¹⁴² Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	190	75/77 0.91 (0.62, 1.35)	unclear	1	no
Goldberg (2006) ¹⁴⁴ 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)	Adequate	3	no
Geiss (2005) ¹¹⁹	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) ¹²⁴ 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
Reckless (2008) ¹⁴⁹ INFORCE International Pharm. Fund Multicentre	CHD patients on previous stable statin dose	Simvastatin 40	213	Double the previous (mixed) statin dose	211	12	92.5	102/96 (0.75, 1.61)	Adequate	2	No
Roeters van Lennep (2008) ¹⁵¹ EASEGO Europe Pharm. Fund Multicentre	CHD and/or controlled type II DM patients not on target LDL-c despite prior low dose simvastatin or atorvastatin therapy	Simvastatin 20	178	Simvastatin 40 or atorvastatin 20	189	12	115	64/66 1.05 (0.68, 1.61)	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
Dagli (2007) ¹⁸⁷ Europe Single center	CHD or risk equivalent with off treatment LDL-c > 210 mg/dL	Pravastatin 10	50	Pravastatin 40	50	24	162	3/6 0.47 (0.11, 1.99)	Unclear	2	Yes
Leiter (2008) ¹⁵⁹ North America Pharm. Fund Multicenter	Participants with or without prior lipid lowering therapy with 10-year CHD risk > 20%	Atorvastatin 40	286	Atorvastatin 80	289	6	89	63/61 1.06 (0.71, 1.57)	Adequate	5	No
Relative probability of participants experiencing an adverse event: all statins, all doses, all clinical populations											
Feldman (2004) ⁴⁷ North America Pharm. Fund Multicenter	Participants with CHD or risk equivalent	Simvastatin 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											
Kastelein (2008) ⁴² ENHANCE International Pharm. fund	FHC LDL-c>190	Simvastatin 80	357	Simvastatin 80	363	96	318	29/34 0.86 (0.51, 1.44)	Adequate	3	no
Ballantyne (2003) ¹²⁶ Ezetimibe Study Group International Pharm. Fund Multicenter	1° 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

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) ¹⁶⁷ 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) ¹²¹ 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) ⁴⁶ 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
Feldman (2004) ⁴⁷ 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) ¹⁵⁴ 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)	Adequate	5	no
Stein (2004) ¹⁵⁶ 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

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) ¹¹¹ Pharm. Fund Multicenter	African descent, 1° HC	Simvastatin 20	124	Simvastatin 20	123	12	176	2/1 2.00 (0.18, 22.35)	Adequate	5	no
Goldberg (2004) ⁴⁸ 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)	Adequate	5	no
Melani (2003) ¹²⁷ 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)	Adequate	4	yes
Kerzner (2003) ¹²⁹ Ezetimibe Study Group North America Pharm. Fund Multicenter	1° 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) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 10	67	Simvastatin 10	70	12	179	2/4 0.51 (0.09, 2.87)	Adequate	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_2) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 20	69	Simvastatin 20	61	12	179	7/6 1.03 (0.33, 3.27)	Adequate	4	no
Davidson (2002_3) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 40	73	Simvastatin 40	65	12	179	3/2 1.35 (0.22, 8.34)	Adequate	4	no
Davidson (2002_4) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 80	65	Simvastatin 80	67	12	179	8/2 4.56 (0.93, 22.36)	Adequate	4	no
Gagne (2002) ¹³² 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) ¹⁶⁸ 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

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
Stein (2008) ¹⁴⁸ International Pharm. fund	HC, Participants with documented statin associated muscle related side effects	Fluvastatin 80	64	Fluvastatin 80	69	12	174	5/6 0.89 (0.26, 3.07)	Adequate	5	yes
Constance (2007) ¹⁹⁴ 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)	Adequate	3	no
Barrios (2005) ¹¹² 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
Cruz- Fernandez (2005) ¹¹⁵ 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) ¹¹⁶ 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) ¹⁴⁰ 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

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) ¹⁴² Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	190	6/3 1.96 (0.48, 7.92)	unclear	1	no
Patel (2006) ¹⁴³ 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) ¹⁴⁴ 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)	Adequate	3	no
Kosoglou (2002) ¹⁰⁶ 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
Roeters van Lennep (2008) ¹⁵¹ EASEGO Europe Pharm. Fund Multicentre	CHD and/or controlled T2DM patients not on target LDL-c despite prior low dose simvastatin or atorvastatin therapy	Simvastatin 20	178	Mixed 20-40	189	12	115	10/7 1.55 (0.58, 4.16)	Unclear	3	No
Dagli (2007) ¹⁸⁷ Europe Single center	CHD or risk equivalent with off treatment LDL-c > 210 mg/dL	Pravastatin 10	50	Pravastatin 40	50	24	162	0/0	Unclear	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
Conrad (2008) ¹⁵⁸ International Pharm. Fund Multicenter	Moderately high risk participants on atorvastatin 20 mg/day or statin naive and with LDL-c 100 mg/dL to <= 160 mg/dL	Atorvastatin 20	96	Atorvastatin 40	98	6	119	0/2 0.20 (0.01, 4.22)	Adequate	5	No
Leiter (2008) ¹⁵⁹ North America Pharm. Fund Multicenter	Participants with or without prior lipid lowering therapy with 10-year CHD risk > 20%	Atorvastatin 40	286	Atorvastatin 80	289	6	89	4/6 0.67 (0.19, 2.40)	Adequate	5	No
Ballantyne (2005) ¹¹⁸ VYVA North America Pharm. Fund Multicenter	Participants with DM not at LDL-c ATP III goal off lipid lowering treatment	Simvastatin 10-80	220	Atorvastatin 10- 80	206	6	178	4/2 1.89 (0.34, 10.42)	Adequate	2	no
Catapno (2006) ¹⁹³ North America Pharm. Fund Multicenter	Participants with DM	Simvastatin 20-80	190	Rosuvastatin 10-40	185	6	173	6/6 0.97 (0.31, 3.07)	Adequate	3	No
Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c >=130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	66	Simvastatin 40	34	4	169	6/1 3.30 (0.38, 28.59)	Adequate	5	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
Relative probability of participants withdrawing from trial due to an adverse event: all statins, lower versus higher doses, all clinical populations											
Gaudiani (2005) ¹²¹ 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) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 10	67	Simvastatin 40	65	12	179	2/2 0.41 (0.08, 2.17)	Adequate	4	no
Davidson (2002_2) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 20	360	Simvastatin 80	253	12	179	18/14 0.90 (0.44, 1.84)	Adequate	4	no
Feldman (2004) ⁴⁷ 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

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
Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c >=130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	66	Simvastatin 40	34	4	169	6/1 3.30 (0.38, 28.59)	Adequate	5	Yes
Relative probability of participants experiencing elevated serum AST and/or ALT ≥ 3 times ULN and/or hepatitis: all statins, all doses, all clinical populations											
Ballantyne (2003) ¹²⁶ Ezetimibe Study Group International Pharm. Fund Multicenter	1° 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) ¹⁶⁷ 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) ⁴⁸ Ezetimibe Study Group International Pharm. fund	1° 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)	Adequate	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
Gaudiani (2005) ¹²¹ 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
Ballantyne (2004) ⁴⁶ 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) ⁴⁷ 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) ¹⁵⁴ North America Pharm. Fund Multicenter	1° 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)	Adequate	5	no
Stein (2004) ¹⁵⁶ International Pharm. fund	1° 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) ¹¹¹ Pharm. Fund Multicenter	African descent, 1° HC	Simvastatin 20	124	Simvastatin 20	123	12	176	0/0	Adequate	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) ¹²⁷ 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	2/1 2.02 (0.18, 22.45)	Adequate	4	yes
Kerzner (2003) ¹²⁹ Ezetimibe Study Group North America Pharm. Fund Multicenter	1° 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) ¹³² 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) ¹⁴⁸ International Pharm. fund	HC, Participants with documented statin associated muscle related side effects	Fluvastatin 80	64	Fluvastatin 80	69	12	174	1/1 1.08 (0.07, 17.62)	Adequate	5	yes
Davidson (2002_1) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 10	61	Simvastatin 10	61	12	179	0/0	Adequate	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_2) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 20	58	Simvastatin 20	53	12	179	1/1 0.91 (0.06, 14.96)	Adequate	4	no
Davidson (2002_3) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 40	68	Simvastatin 40	60	12	179	4/0 8.44 (0.45, 160.12)	Adequate	4	no
Davidson (2002_4) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 80	52	Simvastatin 80	63	12	179	1/1 1.22 (0.07, 19.92)	Adequate	4	no
Constance (2007) ¹⁹⁴ 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)	Adequate	3	no
Cruz- Fernandez (2005) ¹¹⁵ 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

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) ¹¹⁶ 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 (2005) ¹¹⁸ 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)	Adequate	2	no
Blagden (2007) ¹⁴⁰ Europe Pharm. Fund Multicenter	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	0/0	unclear	4	yes
Ballantyne (2007) ¹⁴² Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	190	3/0 6.85 (0.35, 133.38)	unclear	1	no
Goldberg (2006) ¹⁴⁴ 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)	Adequate	3	no
Catapano (2006) ¹⁹³ North America Pharm. Fund Multicenter	Hypercholesterole mia, heterogeneous 10- year CHD risk estimates	Simvastatin 20-80	1437	Rosuvastatin 10-40	1447	6	173	9/3 3.03 (0.82, 11.23)	Adequate	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) ¹¹⁹	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) ¹⁰⁶ North America Pharm. Fund Single centre	Healthy male participants. Low risk	Simvastatin 10	12	Simvastatin 10	12	2	169	0/0	unclear	2	no
Reckless (2008) ¹⁴⁹ INFORCE International Pharm. Fund Multicentre	CHD patients on previous stable statin dose	Simvastatin 40	204	Double the previous (mixed) statin dose	203	12	92.5	6/7 0.85 (0.28, 2.56)	Adequate	2	No
Leiter (2008) ¹⁵⁹ North America Pharm. Fund Multicenter	Participants with or without prior lipid lowering therapy with 10-year CHD risk > 20%	Atorvastatin 40	281	Atorvastatin 80	283	6	89	1/1 1.01 (0.06, 16.14)	Adequate	5	No
Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c >=130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	66	Simvastatin 40	34	4	169	1/0 4.55 (0.07, 285/04)	Adequate	5	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
Relative probability of participants experiencing elevated serum AST and/or ALT ≥ 3 times ULN and/or hepatitis: all statins, lower versus higher doses, all clinical populations											
Gaudiani (2005) ¹²¹ 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) ⁴⁸ Ezetimibe Study Group International Pharm. fund	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 10	134	Simvastatin 40	77	48	175	1/0 1.74 (0.07, 43.28)	Adequate	5	no
Goldberg (2004_2) ⁴⁸ Ezetimibe Study Group International Pharm. fund	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 20	135	Simvastatin 80	73	48	175	1/1 0.54 (0.03, 8.72)	Adequate	5	no
Feldman (2004) ⁴⁷ 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) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 10	61	Simvastatin 40	60	12	179	0/0	Adequate	4	no
Davidson (2002_6) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 20	58	Simvastatin 80	63	12	179	1/1 1.09 (0.07, 17.80)	Adequate	4	no
Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c >=130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	66	Simvastatin 40	34	4	169	1/0 4.55 (0.07, 285/04)	Adequate	5	Yes
Relative probability of participants experiencing myalgia: all statins, all doses, all clinical populations											
Ballantyne (2003) ¹²⁶ Ezetimibe Study Group International Pharm. Fund Multicenter	1° 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) ¹⁶⁷ 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) ⁴⁸ Ezetimibe Study Group International Pharm. fund	1° 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)	Adequate	5	no
Bays (2004) ¹⁵⁴ North America Pharm. Fund Multicenter	1° 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)	Adequate	5	no
Stein (2004) ¹⁵⁶ International Pharm. fund	1° 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) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° 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)	Adequate	4	no
Barrios (2005) ¹¹² 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) ¹¹⁴ 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) ¹⁴⁰ 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) ¹⁴² Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	190	7/7 0.97 (0.33, 2.80)	unclear	1	no
Kosoglou (2004_a) ¹²⁴ Europe Pharm. Fund Single centre	Healthy participants with LDL-c \geq 130 mg/dL and BMI < 31kg/m ² . Low risk	Rosuvastatin 10	12	Rosuvastatin 10	12	2	158	2/2 1.00 (0.12, 8.56)	unclear	2	yes
Kosoglou (2004_b) ¹⁸¹ North America Pharm. Fund Single centre	Healthy participants of European descent with LDL-c \geq 130 mg/dL and BMI < 31kg/m ² . Low risk	Lovastatin 20-40	15	Lovastatin 20	8	2	177	1/0 1.76 (0.06, 48.19)	unclear	1	yes
Kosoglou (2002) ¹⁰⁶ 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) ¹⁰⁹ 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) ¹⁴⁶ 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: all statins, all doses, all clinical populations											
Kastelein (2008) ⁴² 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)	Adequate	3	no
Masana (2005) ¹⁶⁷ 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) ¹⁶⁶ 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	Adequate	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) ¹²¹ 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
Ballantyne (2004) ⁴⁶ 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) ⁴⁷ 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) ¹⁵⁴ North America Pharm. Fund Multicenter	1° 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)	Adequate	5	no
Stein (2004) ¹⁵⁶ International Pharm. fund	1° 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) ¹¹¹ Pharm. Fund Multicenter	African descent, 1° HC	Simvastatin 20	124	Simvastatin 20	123	12	176	0/1 0.33 (0.01, 8.13)	Adequate	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
Goldberg (2004) ⁴⁸ Ezetimibe Study Group International Pharm. fund	1° 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)	Adequate	5	no
Ballantyne (2003) ¹²⁶ Ezetimibe Study Group International Pharm. Fund Multicenter	1° 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) ¹²⁷ 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	0/2 0.20 (0.01, 4.17)	Adequate	4	yes
Kerzner (2003) ¹²⁹ Ezetimibe Study Group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Lovastatin 10-40	192	Lovastatin 10-40	220	12	179	0/0	unclear	3	yes
Davidson (2002) ¹³⁰ Ezetimibe study group North America Pharm. Fund Multicenter	1° 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)	Adequate	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) ¹³⁹ 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) ¹⁶⁸ 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) ¹⁴⁸ International Pharm. fund	HC, Participants with documented statin associated muscle related side effects	Fluvastatin 80	64	Fluvastatin 80	69	12	174	0/0	Adequate	5	yes
Barrios (2005) ¹¹² International Pharm. fund	CHD or risk equivalent	Simvastatin 20	217	Atorvastatin 20	210	6	124	0/0	unclear	3	no
Farnier (2005) ¹¹⁴ 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) ¹¹⁵ 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) ¹¹⁶ 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
Pearson (2005) ¹¹⁷ 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	Adequate	4	no
Ballantyne (2005) ¹¹⁸ 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)	Adequate	2	no
Blagden (2007) ¹⁴⁰ Europe Pharm. Fund Multicenter	Participants with CAD, statin naïve	Atorvastatin 10	72	Atorvastatin 10	76	6	157	0/0	unclear	4	yes
Ballantyne (2007) ¹⁴² Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	190	0/0	unclear	1	no
Goldberg (2006) ¹⁴⁴ 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	Adequate	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) ¹⁹³ 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)	Adequate	3	no
Geiss (2005) ¹¹⁹	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) ¹⁰⁶ North America Pharm. Fund Single centre	Healthy male participants. Low risk	Simvastatin 10	12	Simvastatin 10	12	2	169	0/0	unclear	2	no
Reckless (2008) ¹⁴⁹ INFORCE International Pharm. Fund Multicentre	CHD patients on previous stable statin dose	Simvastatin 40	213	Double the previous (mixed) statin dose	211	12	92.5	0/0	Adequate	2	No
Leiter (2008) ¹⁵⁹ North America Pharm. Fund Multicenter	Participants with or without prior lipid lowering therapy with 10-year CHD risk > 20%	Atorvastatin 40	281	Atorvastatin 80	283	6	89	0/0	Adequate	5	No
Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c >=130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	66	Simvastatin 40	34	4	169	0/0	Adequate	5	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
Relative probability of participants experiencing CPK greater than 10 times the upper limit of normal - all statins, lower versus higher doses, all clinical populations											
Gaudiani (2005) ¹²¹ 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) ⁴⁷ 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 rhabdomyolysis (investigator defined) : all statins, all doses, all clinical populations											
Masana (2005) ¹⁶⁷ 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) ⁴⁸ Ezetimibe Study Group International Pharm. fund	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 10-80	539	Simvastatin 20-80	229	48	175	0/0	Adequate	5	no
Ballantyne (2004) ⁴⁶ 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

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) ⁴⁷ 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) ¹⁵⁴ North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Simvastatin 10-80	544	Simvastatin 10-80	560	14-26	178	0/0	Adequate	5	no
Stein (2004) ¹⁵⁶ International Pharm. fund	1° 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
Rodney (2006) ¹¹¹ Pharm. Fund Multicenter	African descent, 1° HC	Simvastatin 20	124	Simvastatin 20	123	12	176	0/0	Adequate	5	no
Kerzner (2003) ¹²⁹ Ezetimibe Study Group North America Pharm. Fund Multicenter	1° HC, heterogeneous 10- year CHD risk estimates	Lovastatin 10-40	192	Lovastatin 10-40	220	12	179	0/0	unclear	3	yes
Gagne (2002) ¹³² 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

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) ¹⁶⁸ 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) ¹⁴⁸ International Pharm. fund	HC, Participants with documented statin associated muscle related side effects	Fluvastatin 80	64	Fluvastatin 80	69	12	174	0/0	Adequate	5	yes
Barrios (2005) ¹¹² International Pharm. fund	CHD or risk equivalent	Simvastatin 20	221	Atorvastatin 20	214	6	124	0/0	unclear	3	no
Cruz- Fernandez (2005) ¹¹⁵ 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) ¹¹⁶ 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) ¹⁴² Europe Pharm. Fund Multicenter	CHD and risk equivalent	Rosuvastatin 40	238	Rosuvastatin 40	230	6	190	0/0	unclear	1	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
Chenot (2007) ¹⁴⁶ Europe Single centre	Tertiary care patients with acute MI	Simvastatin 40	20	Simvastatin 40	20	1	146	0/0	unclear	1	yes
Farnier (2005) ¹¹⁴ 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
Leiter (2008) ¹⁵⁹ North America Pharm. Fund Multicenter	Participants with or without prior lipid lowering therapy with 10-year CHD risk > 20%	Atorvastatin 40	281	Atorvastatin 80	283	6	89	0/0	Adequate	5	No
Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c >=130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	66	Simvastatin 40	34	4	169	0/0	Adequate	5	Yes
Relative probability of participants experiencing rhabdomyolysis (investigator defined): all statins, lower versus higher doses, all clinical populations											
Feldman (2004) ⁴⁷ 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

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
Dobs (2003) ¹⁶⁹ Pharm. Fund Multicenter	Participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c >=130 mg/dL) not controlled on simvastatin 20 mg/day	Simvastatin 20	66	Simvastatin 40	34	4	169	0/0	Adequate	5	Yes

Included Evidence for Fibrate plus Statin Therapy Compared With Statin Monotherapy

Table F-9. 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) ¹²⁵ 4522IL/0036 Europe Pharm. Fund Multicentre	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 200	113	Rosuvastatin 40	53	18	149	1/1 0.43 (0.02, 8.54)	unclear	2	No
Napoli (1997) ¹⁸⁸ 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) ¹³⁴ Europe Pharm. Fund Multicentre	No specific risk reported	Pravastatin 40	Gemfibrozil 1200	75	Pravastatin 40	71	12	228	0/1 0.13 (0.00, 6.46)	unclear	2	No
Fatal myocardial infarction												
Derosa (2004) ¹²³ 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	Mono therapy 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
Wiklund (1993) ¹³⁴ Europe Pharm. Fund Multicentre	No specific risk reported	Pravastatin 40	Gemfibrozil 1200	75	Pravastatin 40	71	12	228	0/1 0.13 (0.00, 6.46)	unclear	2	No
Non-fatal myocardial infarction												
Derosa (2004) ¹²³ Europe	Participants with combined HC, T2DM and CHD	Fluvastatin 80	Fenofibrate 200	25	Fluvastatin 80	23	52	189	0/0	unclear	3	Yes
Any myocardial infarction												
Derosa (2004) ¹²³ 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) ¹²³ Europe	Participants with combined HC, T2DM and CHD	Fluvastatin 80	Fenofibrate 200	25	Fluvastatin 80	23	52	189	0/0	unclear	3	Yes
Serious adverse event(s)												
Derosa (2004) ¹²³ 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	Mono therapy 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
Grundy (2005) ¹²⁰ 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 F-10. 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) ¹⁶¹	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) ¹²⁵	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 200	113	Rosuvastatin 40	50	18	149	85/43 0.49 (0.20, 1.22)	unclear	2	No

Table F-11. 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 mean percentage change from baseline												
Durrington (2004) ¹²⁵ 4522IL/0036 Europe Pharm. Fund Multicenter	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 10	Fenofibrate 200	53	Rosuvastatin 40	51	18	149	4.50 (-4.10, 13.1)	unclear	2	No
Muhlestein (2006) ¹⁴⁵ DIACOR study North America Pharm. Fund Single center	Participants with mixed dyslipidemia, 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) ¹²⁰ 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 F-12. 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 mean percentage change from baseline												
Durrington (2004) ¹²⁵ 4522IL/0036 Europe Pharm. Fund Multicenter	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 200	113	Rosuvastatin 40	51	18	149	4.81 (-0.56, 10.18)	unclear	2	No
Muhlestein (2006) ¹⁴⁵ DIACOR study North America Pharm. Fund Single center	Participants with mixed dyslipidemia, 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) ¹²⁰ 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 F-13. 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 mean percentage change from baseline												
Durrington (2004) ¹²⁵ 4522IL/0036 Europe Pharm. Fund Multicenter	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 10	Fenofibrate 200	53	Rosuvastatin 40	51	18	149	-2.70 (-10.46, 5.06)	unclear	2	No

Table F-14. Surrogate outcome – Non-HDL-c using fibrate plus statin therapy compared with statin monotherapy

Non-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 mean percentage change from baseline												
Muhlestein (2006) ¹⁴⁵ DIACOR study North America Pharm. Fund Single center	Participants with mixed dyslipidemia, HbA1c <9%, T2DM and without CAD	Simvastatin 20	Fenofibrate 160	100	Simvastatin 20	100	12	278	1.80 (-3.01, 6.61)	unclear	2	Yes

Table F-15. Surrogate outcome – TG using fibrate plus statin therapy compared with statin monotherapy

Tryglicerides												
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 mean percentage change from baseline												
Durrington (2004) ¹²⁵ 4522IL/0036 Europe Pharm. Fund Multicenter	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 10	Fenofibrate 200	113	Rosuvastatin 40	51	18	149	-13.57 (-24.16, -2.98)	unclear	2	No

Table F-16. 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) ¹²³ 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) ¹²⁵ 4522IL/0036 Europe Pharm. Fund Multicenter	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 200	115	Rosuvastatin 40	53	18	149	24/14 0.73 (0.34, 1.57)	unclear	2	no
Wiklund (1993) ¹³⁴ 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) ⁵⁰ 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) ¹⁶¹ 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) ¹²⁵ 4522IL/0036 Europe Pharm. Fund Multicenter	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 200	115	Rosuvastatin 40	53	18	149	2/3 0.29 (0.05, 1.82)	unclear	2	no
Grundy (2005) ¹²⁰ 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) ¹³⁴ 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) ¹⁶⁰	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) ⁵⁰ 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

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) ¹⁶¹ 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
Durrington (2004) ¹²⁵	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 200	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) ⁵⁰	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) ¹⁸⁸	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) ¹²⁵	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 200	115	Rosuvastatin 40	53	18	149	3/1 1.39 (0.14, 13.71)	unclear	2	no
Grundy (2005) ¹²⁰	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) ¹³⁴	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

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
Shah (2007_1) ¹⁹⁵	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) ¹⁹⁵		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												
Athyros (2002) ¹⁶¹	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) ¹²⁵	Participants with combined HC, HbA1c <10%, and T2DM	Rosuvastatin 5-10	Fenofibrate 200	115	Rosuvastatin 40	53	18	149	0/0	unclear	2	no
Grundy (2005) ¹²⁰	Combined HC, 71% with MetS	Simvastatin 20	Fenofibrate 160	403	Simvastatin 20	202	12	163	1/0 4.49 (0.07, 286.36)	yes	2	no
Muhlestein (2006) ¹⁴⁵	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

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
Wiklund (1993) ¹³⁴	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) ¹²⁰	Combined HC, 71% with MetS	Simvastatin 20	Fenofibrate 160	403	Simvastatin 20	202	12	163	0/0	yes	2	no
Wiklund (1993) ¹³⁴	No particular risk described	Pravastatin 40	Gemfibrozil 1200	75	Pravastatin 40	71	12	228	0/0	unclear	2	no
Muhlestein (2006) ¹⁴⁵	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 F-17. 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 – patients requiring intensive lipid lowering therapy												
Taylor (2004) ¹⁹⁶ 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 RIs	78	Mixed >20	71	52	89	2/1 1.84 (0.16, 20.76)	yes	5	No
All-cause mortality												
Taylor (2004) ¹⁹⁶ 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 RIs	78	Mixed >20	71	52	89	2/1 1.84 (0.16, 20.76)	yes	5	No
Kos Pharm (MA-06) ¹⁰⁵ MA-06 North America Multicenter	Participants with hyperlipidemi a type IIa or IIb, Statin naïve	Lovastatin 40	Ext RIs	114	Lovastatin 40	61	28	189	1/1 0.53 (0.03, 8.64)	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
Kos Pharm (MA-14) ¹⁰⁴ MA-14 North America Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia) ; Statin naïve.	Lovastatin 10	Ext RIs	100	Lovastatin 40	33	20	198	0/0	yes	4	No
Stein (1996) ¹⁷⁰ North America Pharm. Fund Multicenter	Participants with elevated low-density lipoprotein cholesterol, high triglycerides, and low high- density lipoprotein cholesterol	Simvastatin 10	Imm RIs	60	Simvastatin 10	60	17	176	0/0	unclear	2	No
Ballantyne (2008_a) ¹⁵⁰ North America, South America, Europe Pharm. Fund Multicenter	Participants with increased ATP III risk adjusted non- HDL-c but on target LDL-c on run-in simvastatin 20 mg/day	Simvastatin 20	Ext RIs 1000-2000	187	Simvastatin 20	114	24		0/0	unclear	3	No
Ballantyne (2008_b) ¹⁷¹ North America, South America, Pharm. Fund Multicenter	Participants with elevated non-HDL-c level despite run-in simvastatin 40 mg/day	Simvastatin 40	Ext RIs 1000-2000	216	Simvastatin 80	119	24		0/0	adequate	3	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
All-cause mortality – Adequate Allocation Concealment												
Taylor (2004) ¹⁹⁶ 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 RIs	78	Mixed >20	71	52	89	2/1 1.84 (0.16, 20.76)	yes	5	No
Kos Pharm (MA-06) ¹⁰⁵ MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 40	Ext RIs	114	Lovastatin 40	61	28	189	1/1 0.53 (0.03, 8.64)	yes	5	No
Kos Pharm (MA-14) ¹⁰⁴ MA-14 North America Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia) ; Statin naïve.	Lovastatin 10	Ext RIs	100	Lovastatin 40	33	20	198	0/0	yes	4	No
Ballantyne (2008_b) ¹⁷¹ North America, South America, Pharm. Fund Multicenter	Participants with elevated non-HDL-c level despite run-in simvastatin 40 mg/day	Simvastatin 40	Ext RIs	216	Simvastatin 80	119	24		0/0	adequate	3	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
All-cause mortality – patients with vascular disease												
Taylor (2004) ¹⁹⁶ 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 RIs	78	Mixed >20	71	52	89	2/1 1.84 (0.16, 20.76)	yes	5	No
Vascular death – patients requiring intensive lipid lowering therapy												
Kuvin (2006) ¹⁹⁷ 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 RIs	27	Mixed	27	12	79	0/0	unclear	1	No
Vascular death												
Hunninghake (2003) ¹²⁸ North America Pharm. Fund Multicenter	Participants with type IIA hyperlipidemia or type IIB hyperlipidemia	Lovastatin 40	Ext RIs	114	Lovastatin 40	61	28	189	1/1 0.53 (0.03, 8.64)	unclear	4	Yes
Kuvin (2006) ¹⁹⁷ 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 RIs	27	Mixed	27	12	79	0/0	unclear	1	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
Vascular death – patients with vascular disease												
Kuin (2006) ¹⁹⁷ 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 RIs	27	Mixed	27	12	79	0/0	unclear	1	No
Fatal myocardial infarction												
Kos Pharm (MA-06) ¹⁰⁵ MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 40	Ext RIs	114	Lovastatin 40	61	28	189	1/0 1.63 (0.07, 40.51)	yes	5	No
Kuin (2006) ¹⁹⁷ 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 RIs	27	Mixed	27	12	79	0/0	unclear	1	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
Any stroke												
Taylor (2004) ¹⁹⁶ 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 RIs	78	Mixed >20	71	52	89	0/1 0.12 (0.00, 6.21)	yes	5	No
Acute coronary syndrome												
Taylor (2004) ¹⁹⁶ 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 RIs	78	Mixed >20	71	52	89	2/2 0.91 (0.12, 6.62)	yes	5	No
Percutaneous coronary intervention												
Taylor (2004) ¹⁹⁶ 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 RIs	78	Mixed >20	71	52	89	4/1 3.78 (0.41, 34.68)	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
Serious adverse events												
Kos Pharm (MA-06) ¹⁰⁵ MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 20-40	Ext RIs	114	Lovastatin 40	61	28	189	5/2 1.35 (0.25, 7.19)	yes	5	No
Kos Pharm (MA-14) ¹⁰⁴ MA-14 North America Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia) ; Statin naïve.	Lovastatin 10-40	Ext RIs	100	Lovastatin 40	33	20	198	5/1 1.68 (0.19, 14.96)	yes	4	No
Stein (1996) ¹⁷⁰ North America Pharm. Fund Multicentre	Participants with elevated low-density lipoprotein cholesterol, high triglycerides, and low high- density lipoprotein cholesterol	Simvastatin 10	Imm RIs	60	Simvastatin 10	60	17	176	1/0 3.05 (0.12, 76.39)	unclear	2	No
Ballantyne (2008_a) ¹⁵⁰ North America, South America, Europe Pharm. Fund Multicenter	Participants with increased ATP III risk adjusted non- HDL-c but on target LDL-c on run-in simvastatin 20 mg/day	Simvastatin 20	Ext RIs	187	Simvastatin 20	114	24		1/0 1.84 (0.07, 45.60)	unclear	3	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
Ballantyne (2008_b) ¹⁷¹ North America, South America, Pharm. Fund Multicenter	Participants with elevated non-HDL-c level despite run-in simvastatin 40 mg/day	Simvastatin 40	Ext RIs	216	Simvastatin 80	119	24	104	0/1 0.18 (0.01, 4.51)	adequate	3	No
Cancer												
Kos Pharm (MA-06) ¹⁰⁵ MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 20-40	Ext RIs	114	Lovastatin 40	61	28	189	0/2 0.10 (0.00, 2.2)	yes	5	No

Table F-18. 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 ATP-III LDL-c target - Participants requiring intensive lipid lowering therapy												
Bays (2003) ⁴⁹ 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
Relative probability of attaining ATP-III LDL-c target												
Bays (2003_1) ⁴⁹ 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) ⁴⁹ 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

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Mono 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 - Participants with vascular disease												
Bays (2003) ⁴⁹ 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 F-19. 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 percentage change from baseline - Rosuvastatin Lower dose statin in combination versus higher dose monotherapy												
Capuzzi (2003) ¹⁵⁵ 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10	Ext RIs	78	Rosuvastatin 40	46	24	145	12.00 (2.26, 21.74)	unclear	2	No
Difference in mean percentage change from baseline - Participants requiring intensive lipid lowering therapy												
Moore (2007) ¹⁶² North America, Pharm. Fund Single icenter	Participants with increased ATP III risk adjusted non-HDL-c but on target LDL-c on run-in simvastatin 20 mg/day	Atorvastatin 20	Ext RIs	41	Atorvastatin 30	42	48	154	0 (-6.51, 6.51)	unclear	2	Yes
Difference in mean percentage change from baseline												
Kos Pharm (MA- 06) ¹⁰⁵ MA-06 North America Multicenter	Participants with hyperlipidem ia type IIa or IIb, Statin naïve	Lovastatin 40	Ext RIs	42	Lovastatin 40	53	28	189	-9.70 (-14.64, -4.76)	yes	5	No
Capuzzi (2003) ¹⁵⁵ 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10-40	Ext RIs	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	Mono therapy 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) ¹⁸² North America Pharm. Fund Multicenter	Participants with type IIa or IIb primary hyperlipidemia, statin naïve	Lovastatin 40	Ext RIs	32	Lovastatin 40	33	20	198	-22.20 (-32.09, - 12.31)	unclear	2	No
Kos Pharm (MA- 14) ¹⁰⁴ MA-14 North America Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia) ; Statin naïve.	Lovastatin 40	Ext RIs	23	Lovastatin 40	29	20	198	-22.20 (-31.64, - 12.76)	yes	4	No
McKenney (2007_2) ¹³⁹ COMPELL study North America Pharm. Fund Multicenter	HC, heterogeneous 10-year CHD risk estimates	Atorvastatin 40	Ext RIs	60	Rosuvastatin 40	73	12	197	-3.00 (-8.30, 2.30)	unclear	2	No
Vacek (1995) ¹⁸⁴ 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
Moore (2007) ¹⁶² North America, Pharm. Fund Single center	Participants with increased ATP III risk adjusted non- HDL-c but on target LDL-c on run-in simvastatin 20 mg/day	Atorvastatin 20	Ext RIs	41	Atorvastatin 30	42	48	154	0 (-6.51, 6.51)	unclear	2	Yes

Table F-20. 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)	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 percentage change from baseline – Participants requiring intensive lipid lowering												
Moore (2007) ¹⁶² North America, Pharm. Fund Single center	Participants with increased ATP III risk adjusted non-HDL-c but on target LDL-c on run-in simvastatin 20 mg/day	Atorvastatin 20	Ext RIs	41	Atorvastatin 30	42	48	154	13.00 (6.01, 19.99)	unclear	2	Yes
Difference in mean percentage change from baseline												
Kos Pharm (MA-06) ¹⁰⁵ MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 40	Ext RIs	42	Lovastatin 40	53	28	189	24.00 (17.50, 30.50)	yes	5	no
Capuzzi (2003) ¹⁵⁵ 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 40	Ext RIs	71	Rosuvastatin 40	46	24	145	6.00 (-0.79, 12.79)	unclear	2	no
Insull (2004) ¹⁸² 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) ¹⁰⁴ 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) ¹³⁹ COMPELL study North America Pharm. Fund Multicenter	HC, heterogeneous 10-year CHD risk estimates	Mixed 20-40	Ext RIs	125	Rosuvastatin 40	73	12	197	16.00 (11.43, 20.57)	unclear	2	no
Moore (2007) ¹⁶² North America, Pharm. Fund Single center	Participants with increased ATP III risk adjusted non-HDL-c but on target LDL-c on run-in simvastatin 20 mg/day	Atorvastatin 20	Ext RIs	41	Atorvastatin 30	42	48	154	13.00 (6.01, 19.99)	unclear	2	Yes
Difference in mean percentage change from baseline - Rosuvastatin Lower dose statin in combination versus higher dose monotherapy												
Capuzzi (2003) ¹⁵⁵ 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	13.00 (6.10, 19.90)	unclear	2	no

Table F-21. 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 mean percentage change in TC:HDL-c ratio												
McKenney (2007_2) ¹³⁹	HC, heterogeneous 10-year CHD risk estimates	Mixed 20-40	Ext RIs 2000	125	Rosuvastatin 40	73	12	197	-6.00 (-9.60, - 2.40)	unclear	2	no

Table F-22. 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) ¹⁹⁶ 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 RIs 1000	71	Mixed >20	78	52	89	-0.03 (-0.06, 0.00)	yes	5	no

Table F-23. 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) ¹⁹⁶ 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 RIs 1000	87	Mixed >20	80	52	89	78/71 1.10 (0.41, 2.92)	yes	5	no
Capuzzi (2003) ¹⁵⁵ 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10-40	Ex RIs 2000	152	Rosuvastatin 40	46	24	145	71/31 0.42 (0.21, 0.85)	unclear	2	no
Insull (2004) ¹⁸² 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) ⁴⁹ ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex RIs 2000	78	Simvastatin 10-40	76	16	192	73/73 0.60 (0.14, 2.60)	unclear	1	no
Bays (2003_2) ⁴⁹ ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex RIs 2000	79	Atorvastatin 10-40	82	16	192	77/79 1.46 (0.24, 8.99)	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
McKenney (2007_2) ¹³⁹ COMPELL study North America Pharm. Fund Multicenter	HC, heterogeneous 10-year CHD risk estimates	Mixed 20-40	Ex RIs 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												
Taylor (2004) ¹⁹⁶ 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 RIs 1000	87	Mixed >20	80	52	89	78/71 1.10 (0.41, 2.92)	yes	5	no
Capuzzi (2003) ¹⁵⁵ 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10-40	Ex RIs 2000	152	Rosuvastatin 40	46	24	145	71/31 0.42 (0.21, 0.85)	unclear	2	no
Relative probability of participants adhering to treatment – Rosuvastatin - Lower dose statin in combination versus higher dose monotherapy												
Capuzzi (2003) ¹⁵⁵ 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10	Ex RIs 2000	80	Rosuvastatin 40	46	24	145	36/31 0.42 (0.19, 0.84)	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
Relative probability of participants experiencing an adverse event												
Kos Pharm (MA-06) ¹⁰⁵ MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 20-40	Ex RIs 2000	114	Lovastatin 40	61	28	189	110/49 6.73 (2.07, 21.93)	yes	5	no
Capuzzi (2003) ¹⁵⁵ 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10-40	Ex RIs 2000	152	Rosuvastatin 40	46	24	145	129/34 1.98 (0.90, 4.38)	unclear	2	no
Insull (2004) ¹⁸² North America Pharm. Fund Multicenter	Participants with type IIa or IIb primary hyperlipidemia, statin naïve	Lovastatin 10-40	Ex RIs 2500	100	Lovastatin 40	33	20	198	53/17 1.06 (0.48, 2.33)	unclear	2	no
Kos Pharm (MA-14) ¹⁰⁴ MA-14 North America Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia); Statin naïve.	Lovastatin 10-40	Ex RIs 2500	100	Lovastatin 40	33	20	198	88/24 2.75 (1.04, 7.29)	yes	4	no
Ballantyne (2008_a) ¹⁵⁰ North America, South America, Europe Pharm. Fund Multicenter	Participants with increased ATP III risk adjusted non-HDL-c but on target LDL-c on run-in simvastatin 20 mg/day	Simvastatin 20	Ext RIs 1000-2000	187	Simvastatin 20	114	24		54/20 1.91 (1.07, 3.40)	unclear	3	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
Ballantyne (2008_b) ¹⁷¹ North America, South America, Pharm. Fund Multicenter	Participants with elevated non- HDL-c level despite run-in simvastatin 40 mg/day	Simvastatin 40	Ext RIs 1000-2000	216	Simvastatin 80	119	24	104	68/35 1.10 (0.68, 1.80)	adequate	3	No
Relative probability of participants experiencing an adverse event – 24 weeks or longer follow-up												
Kos Pharm (MA-06) ¹⁰⁵ MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 20-40	Ex RIs 2000	114	Lovastatin 40	61	28	189	110/49 6.73 (2.07, 21.93)	yes	5	no
Capuzzi (2003) ¹⁵⁵ 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10-40	Ex RIs 2000	152	Rosuvastatin 40	46	24	145	129/34 1.98 (0.90, 4.38)	unclear	2	no
Ballantyne (2008_a) ¹⁵⁰ North America, South America, Europe Pharm. Fund Multicenter	Participants with increased ATP III risk adjusted non-HDL-c but on target LDL-c on run-in simvastatin 20 mg/day	Simvastatin 20	Ext RIs 1000-2000	187	Simvastatin 20	114	24		54/20 1.91 (1.07, 3.40)	unclear	3	No
Ballantyne (2008_b) ¹⁷¹ North America, South America, Pharm. Fund Multicenter	Participants with elevated non- HDL-c level despite run-in simvastatin 40 mg/day	Simvastatin 40	Ext RIs 1000-2000	216	Simvastatin 80	119	24	104	68/35 1.10 (0.68, 1.80)	adequate	3	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
Relative probability of participants experiencing an adverse event – Rosuvastatin - Lower dose statin in combination versus higher dose monotherapy												
Capuzzi (2003) ¹⁵⁵ 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10	Ex RIs 2000	78	Rosuvastatin 40	46	24	145	66/34 1.94 (0.79, 4.78)	unclear	2	no
Relative probability of participants withdrawing from treatment due to an adverse event												
Taylor (2004) ¹⁹⁶ 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 RIs 1000	87	Mixed >20	80	52	89	2/6 0.29 (0.06, 1.48)	yes	5	no
Hunninghake (2003) ¹²⁸ North America Pharm. Fund Multicenter	Participants with type IIA hyperlipidemia or type IIB hyperlipidemia	Lovastatin 20-40	Ex RIs 2000	114	Lovastatin 40	61	28	189	22/6 2.19 (0.84, 5.74)	unclear	4	yes
Kos Pharm (MA- 06) ¹⁰⁵ MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 20-40	Ex RIs 2000	114	Lovastatin 40	61	28	189	22/6 2.19 (0.84, 5.74)	yes	5	no
Insull (2004) ¹⁸² North America Pharm. Fund Multicenter	Participants with type IIa or IIb primary hyperlipidemia, statin naïve	Lovastatin 10-40	Ex RIs 2500	100	Lovastatin 40	33	20	198	18/3 2.20 (0.60, 7.99)	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
Kos Pharm (MA-14) ¹⁰⁴ MA-14 North America Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia); Statin naïve.	Lovastatin 10-40	Ex RIs 2500	100	Lovastatin 40	33	20	198	18/3 2.20 (0.60, 7.99)	yes	4	no
O'Keefe (1995) ¹⁸⁹ 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 RIs 3000	27	Pravastatin 20	19	18	134	6/0 11.79 (0.62, 223.26)	unclear	1	no
Stein (1996) ¹⁷⁰ North America Pharm. Fund Multicenter	Participants with elevated low-density lipoprotein cholesterol, high triglycerides, and low high-density lipoprotein cholesterol	Simvastatin 10	Imm RIs 1500	60	Simvastatin 10	60	17	176	9/3 3.35 (0.86, 13.07)	unclear	2	no
Bays (2003_1) ⁴⁹ ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex RIs 2000	78	Simvastatin 10-40	76	16	192	15/2 8.81 (1.94, 40.01)	unclear	1	no
Bays (2003_2) ⁴⁹ ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex RIs 2000	79	Atorvastatin 10-40	82	16	192	13/8 1.82 (0.71, 4.67)	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
Ballantyne (2008_a) ¹⁵⁰ North America, South America, Europe Pharm. Fund Multicenter	Participants with increased ATP III risk adjusted non-HDL-c but on target LDL-c on run-in simvastatin 20 mg/day	Simvastatin 20	Ext RIs 1000-2000	187	Simvastatin 20	114	24		25/6 2.78 (1.10, 7.00)	unclear	3	No
Ballantyne (2008_b) ¹⁷¹ North America, South America, Pharm. Fund Multicenter	Participants with elevated non- HDL-c level despite run-in simvastatin 40 mg/day	Simvastatin 40	Ext RIs 1000-2000	216	Simvastatin 80	119	24	104	25/5 2.98 (1.11, 8.01)	adequate	3	No
Relative probability of participants experiencing Rhabdomyolysis												
Kos Pharm (MA-06) ¹⁰⁵ MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 20-40	Ex RIs 2000	114	Lovastatin 40	61	28	189	0/0	yes	5	no
Kos Pharm (MA-14) ¹⁰⁴ MA-14 North America Multicenter	HC type IIa or IIb statin naïve	Lovastatin 10-40	Ex RIs 2500	100	Lovastatin 40	33	20	198	0/0	yes	4	no
Ballantyne (2008_a) ¹⁵⁰ North America, South America, Europe Pharm. Fund Multicenter	Participants with increased ATP III risk adjusted non-HDL-c but on target LDL-c on run-in simvastatin 20 mg/day	Simvastatin 20	Ext RIs 1000-2000	187	Simvastatin 20	114	24		0/0	unclear	3	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
Ballantyne (2008_b) ¹⁷¹ North America, South America, Pharm. Fund Multicenter	Participants with elevated non- HDL-c level despite run-in simvastatin 40 mg/day	Simvastatin 40	Ext RIs 1000-2000	216	Simvastatin 80	119	24	104	0/0	adequate	3	No
Relative probability of participants experiencing elevated serum AST and/or ALT > 3 times ULN and/or hepatitis												
Taylor (2004) ¹⁹⁶ 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 RIs 1000	78	Mixed >20	71	52	89	0/0	yes	5	no
Hunninghake (2003) ¹²⁸ North America Pharm. Fund Multicenter	Participants with type IIA hyperlipidemia or type IIB hyperlipidemia	Lovastatin 20-40	Ex RIs 2000	114	Lovastatin 40	61	28	189	1/1 0.53 (0.03, 8.64)	unclear	4	yes
Capuzzi (2003) ¹⁵⁵ 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10-40	Ex RIs 2000	152	Rosuvastatin 40	46	24	145	0/0	unclear	2	no
Insull (2004) ¹⁸² North America Pharm. Fund Multicenter	Participants with type IIa or IIb primary hyperlipidemia, statin naïve	Lovastatin 10-40	Ex RIs 2500	100	Lovastatin 40	33	20	198	4/0 3.12 (0.16, 59.58)	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
Kos Pharm (MA-14) ¹⁰⁴ MA-14 North America Multicenter	HC type IIa or IIb statin naive	Lovastatin 10-40	Ex RIs 2500	100	Lovastatin 40	33	20	198	4/0 3.12 (0.16, 59.58)	yes	4	no
Stein (1996) ¹⁷⁰ North America Pharm. Fund Multicenter	Participants with elevated low- density lipoprotein cholesterol, high triglycerides, and low high-density lipoprotein cholesterol	Simvastatin 10	Imm RIs 1500	60	Simvastatin 10	60	17	176	0/1 0.33 (0.01, 8.21)	unclear	2	no
Bays (2003_1) ⁴⁹ ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex RIs 2000	78	Simvastatin 10-40	76	16	192	0/0	unclear	1	no
Bays (2003_2) ⁴⁹ ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex RIs 2000	79	Atorvastatin 10-40	82	16	192	0/0	unclear	1	no
Ballantyne (2008_a) ¹⁵⁰ North America, South America, Europe Pharm. Fund Multicenter	Participants with increased ATP III risk adjusted non-HDL-c but on target LDL-c on run-in simvastatin 20 mg/day	Simvastatin 20	Ext RIs 1000-2000	187	Simvastatin 20	114	24		0/0	unclear	3	No

Trial	Population	Combination Statin Dose (mg/day)	Niacin Max Dose (mg/day)	Combo N	Mono therapy 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
Ballantyne (2008_b) ¹⁷¹ North America, South America, Pharm. Fund Multicenter	Participants with elevated non- HDL-c level despite run-in simvastatin 40 mg/day	Simvastatin 40	Ext RIs 1000-2000	216	Simvastatin 80	119	24	104	0/0	adequa te	3	No
Moore (2007) ¹⁶² North America, Pharm. Fund Single center	Participants with increased ATP III risk adjusted non-HDL-c but on target LDL-c on run-in simvastatin 20 mg/day	Atorvastatin 20	Ext RIs	41	Atorvastatin 30	42	48	154	1/0 3.15 (0.12, 79.54)	unclear	2	Yes
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) ¹⁵⁵ 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10	Ex RIs 2000	80	Rosuvastatin 40	46	24	145	0/0	unclear	2	no
Relative probability of participants experiencing myalgia												
Hunninghake (2003) ¹²⁸ North America Pharm. Fund Multicenter	Participants with type IIA hyperlipidemia or type IIB hyperlipidemia	Lovastatin 20-40	Ex RIs 2000	114	Lovastatin 40	61	28	189	5/4 0.65 (0.17, 2.53)	unclear	4	yes
Kos Pharm (MA- 06) ¹⁰⁵ MA-06 North America Multicenter	Participants with hyperlipidemia type IIA or IIB, Statin naïve	Lovastatin 20-40	Ex RIs 2000	114	Lovastatin 40	61	28	189	5/7 0.35 (0.11, 1.17)	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
Bays (2003_1) ⁴⁹ ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex RIs 2000	78	Simvastatin 10-40	76	16	192	0/0	unclear	1	no
Bays (2003_2) ⁴⁹ ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex RIs 2000	79	Atorvastatin 10-40	82	16	192	0/1 0.34 (0.01, 8.51)	unclear	1	no
Relative probability of participants experiencing CPK greater than 10 times the upper limit of normal												
Kos Pharm (MA-06) ¹⁰⁵ MA-06 North America Multicenter	Participants with hyperlipidemia type IIa or IIb, Statin naïve	Lovastatin 40	Ex RIs 2000	114	Lovastatin 40	61	28	189	0/0	yes	5	no
Capuzzi (2003) ¹⁵⁵ 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10-40	Ex RIs 2000	152	Rosuvastatin 40	46	24	145	0/0	unclear	2	no
Insull (2004) ¹⁸² North America Pharm. Fund Multicenter	Participants with type IIa or IIb primary hyperlipidemia, statin naïve	Lovastatin 10-40	Ex RIs 2500	100	Lovastatin 40	33	20	198	0/0	unclear	2	no
Kos Pharm (MA-14) ¹⁰⁴ MA-14 North America Multicenter	HC type IIa or IIb statin naïve	Lovastatin 10-40	Ex RIs	100	Lovastatin 40	33	20	198	0/0	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
Bays (2003_1) ⁴⁹ ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex RIs 2000	78	Simvastatin 10-40	76	16	192	0/0	unclear	1	no
Bays (2003_1) ⁴⁹ ADVOCATE North America Pharm. Fund Multicenter	Participants with elevated LDL-c and decreased HDL-c blood levels	Lovastatin 20-40	Ex RIs 2000	79	Atorvastatin 10-40	82	16	192	0/0	unclear	1	no
McKenney (2007_2) ¹³⁹ COMPELL study North America Pharm. Fund Multicenter	HC, heterogeneous 10-year CHD risk estimates	Mixed 20-40	Ex RIs 2000	125	Rosuvastatin 40	73	12	197	0/0	unclear	2	no
Stein (1996) ¹⁷⁰ North America Pharm. Fund Multicenter	Participants with elevated low- density lipoprotein cholesterol, high triglycerides, and low high-density lipoprotein cholesterol	Simvastatin 10	Imm RIs 1500	60	Simvastatin 10	60	17	176	0/0	unclear	2	no
Moore (2007) ¹⁶² North America, Pharm. Fund Single center	Participants with increased ATP III risk adjusted non-HDL-c but on target LDL-c on run-in simvastatin 20 mg/day	Atorvastatin 20	Ext RIs	41	Atorvastatin 30	42	48	154	1/0 3.15 (0.12, 79.54)	unclear	2	Yes

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
Ballantyne (2008_b) ¹⁷¹ North America, South America, Pharm. Fund Multicenter	Participants with elevated non- HDL-c level despite run-in simvastatin 40 mg/day	Simvastatin 40	Ext RIs 1000-2000	216	Simvastatin 80	119	24	104	0/0	ade- quate	3	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) ¹⁵⁵ 4522IL/0029 North America Pharm. Fund Multicenter	Participants with combined dyslipidemia (Fredrickson's type IIb or IV hyperlipidemia)	Rosuvastatin 10	Ex RIs 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 F-24. 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) ⁵² North America Pharm. Fund Multicentre	Participants with moderate HC (LDL-c ≥ 160 mg/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) ⁵² North America Pharm. Fund Multicentre	Participants with moderate HC (LDL-c ≥ 160 mg/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) ¹⁷² North America Pharm. Fund Multicentre	Participants with moderate HC (LDL-c ≥ 160 mg/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) ¹⁷² 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) ¹⁸⁵ 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) ⁵² 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) ⁵² 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

Trial	Population	Combination Statin Dose (mg/day)	BAS (mg/day)	Combo N	Mono therapy 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)												
Simons (1998) ¹⁹⁸ 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) ¹⁷² 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 F-25. 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) ¹⁰⁸ 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 F-26. 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 mean percentage change from baseline												
Hunninghake (2001) ¹³³ North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥ 160 mg/dL)	Atorvastatin 10	C-lam 3.8g	18	Atorvastatin 80	20	4	184	5 (-3.34, 13.34)	unclear	4	yes
O'Brien (1990) ¹⁷⁴ 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) ¹⁶³ 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) ¹⁹⁸ 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) ⁵² North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥ 160 mg/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) ⁵² North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥ 160 mg/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) ¹⁹¹ 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) ¹⁷³ 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) ¹⁶⁴ 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) ¹²² 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) ¹⁷² 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) ¹⁷² 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) ¹³³ 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) ¹⁸⁵ 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 F-27. Surrogate outcome – HDL-c using BAS plus statin therapy compared with statin monotherapy

High 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 mean percentage change from baseline												
Hunninghake (2001) ¹³³ North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥160mg/dL)	Atorvastatin 10	C-lam 3.8g	18	Atorvastatin 80	20	4	184	5 (-3.34, 13.34)	unclear	4	yes
O'Brien (1990) ¹⁷⁴ 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) ¹⁶³ 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) ¹⁹⁸ 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) ⁵² 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) ⁵² 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) ¹⁹¹ Pravastatin Multicenter Study Group II North America Pharm. fund	Participants with moderate HC (LDL-c ≥ 160 mg/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) ¹⁷³ 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) ¹⁶⁴ Multicenter	Participants with moderate HC (LDL-c ≥ 160 mg/dL)	Atorvastatin 10	C-pol 20	40	Atorvastatin 10	41	11	211	1.00 (-6.03, 8.0)	unclear	1	no
Ballantyne (2004_a) ¹²² 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) ¹⁸⁵ North America Pharm. Fund Multicenter	Participants with moderate HC (LDL-c ≥ 160 mg/dL)	Lovastatin 10	C-lam 3.8g	50	Lovastatin 10	26	4	170	0.00 (-4.77, 4.8)	unclear	4	no

Table F-28. 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) ¹⁹⁰ PaCt trial Europe Pharm. Fund Multicenter	Participants with 1 ^o 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) ¹⁶⁴ 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) ¹²² 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) ¹³⁷ 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) ¹³³ 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	Mono therapy 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) ¹³³ 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) ⁵² 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) ⁵² 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) ¹²² 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) ¹⁷² 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	Mono 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) ¹⁷² 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) ¹³⁷ 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) ¹⁹⁸ 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) ⁵² 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	1/4 0.25 (0.03, 2.32)	unclear	3	no
PMSG II (1993) ¹⁹¹ 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

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
Heinonen (1996) ¹⁶⁴ 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
Ballantyne (2004_a) ¹²² 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) ¹⁷² 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) ¹⁷² 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) ¹⁸⁵ 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) ¹³³ 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

Trial	Population	Combination Statin Dose (mg/day)	BAS Max Dose (mg/day)	Combo N	Mono 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) ¹³³ 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
Relative probability of participants experiencing elevated serum AST and/or ALT > 3 times ULN and/or hepatitis												
Simons (1998) ¹⁹⁸ 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) ¹⁸⁵ 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) ¹⁰⁸ 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) ¹⁷³ 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) ¹²²	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

Trial	Population	Combination Statin Dose (mg/day)	BAS Max Dose (mg/day)	Combo N	Mono 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 (2001) ¹⁸⁵ 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												
Simons (1998) ¹⁹⁸ 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) ¹²² 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 F-29. 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) ¹⁴¹ 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) ¹⁸⁰ 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) ¹⁷⁷ 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) ¹⁴¹ 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) ¹⁴¹ 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) ¹⁸⁰ 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) ¹⁴¹ 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 – Participants requiring intensive lipid lowering therapy											
Durrington (2001) ¹⁷⁶ 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 0.12 (0.00, 6.11)	unclear	3	no

Fatal Myocardial Infarction											
Yokoyama (2007) ¹⁴¹ JELIS Asia Pharm. Fund Multicenter	Participants with hypercholesterolemia in Japan	Mixed 5-20	9326	Mixed 5-20	9319	240	182	11/14 0.79 (0.36, 1.72)	yes	2	yes
Durrington (2001) ¹⁷⁶ 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 0.12 (0.00, 6.11)	unclear	3	no
Non-fatal myocardial infarction											
Yokoyama (2007) ¹⁴¹ JELIS Asia Pharm. Fund Multicenter	Participants with hypercholesterolemia in Japan	Mixed 5-20	9326	Mixed 5-20	9319	240	182	62/83 0.75 (0.54, 1.03)	yes	2	yes
Any myocardial infarction											
Yokoyama (2007) ¹⁴¹ 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) ¹⁴¹ JELIS Asia Pharm. Fund Multicenter	Participants with hypercholesterolemia in Japan	Mixed 5-20	9326	Mixed 5-20	9319	240	182	49/39 0.42 (0.10, 1.87)	yes	2	yes

Ischemic stroke											
Yokoyama (2007) ¹⁴¹ 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) ¹⁴¹ 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) ¹⁸⁰ 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) ¹⁴¹ 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 F-30. 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 percentage change from baseline											
Davidson (2007) ¹⁸⁰ 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) ¹⁰⁷ 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 F-31. 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 percentage change from baseline HDL-c											
Davidson (2007) ¹⁸⁰ 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) ¹⁰⁷ 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) ¹⁷⁸ 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 F-32. 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 mean percentage change in TC:HDL-c ratio											
Davidson (2007) ¹⁸⁰ 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) ¹⁷⁸ 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 F-33. 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) ¹⁴¹ 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) ¹⁷⁶ 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) ¹⁷⁹ 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) ¹⁸⁰ 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) ¹⁶⁵ 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) ¹⁷⁷ 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

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 - Trials 24 weeks or longer												
Yokoyama (2007) ¹⁴¹ 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) ¹⁷⁶ 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) ¹⁸⁰ 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) ¹⁸⁰ 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) ¹⁶⁵ 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) ¹⁷⁷ 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) ¹⁸⁰ 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) ¹⁶⁵ 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) ¹⁷⁷ 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) ¹⁸⁰ 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 G: Forest and Funnel Plots

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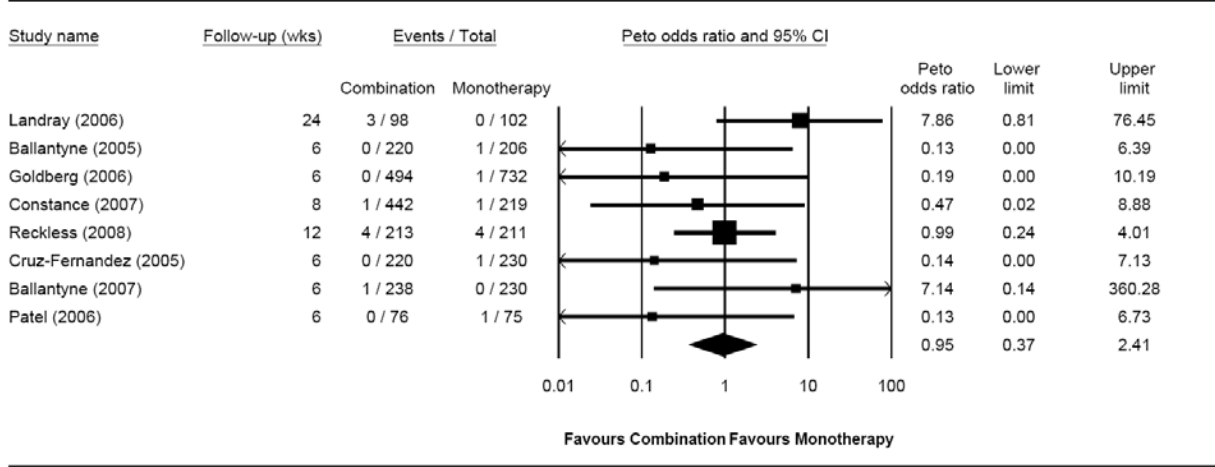
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Forest and Funnel Plots: Ezetimibe - Statin Combination Therapy Versus Statin Monotherapy

Figure G-1. Forest and funnel plots of all-cause mortality for ezetimibe plus statin therapy compared with statin monotherapy in all participants



$I^2 = 13.33$

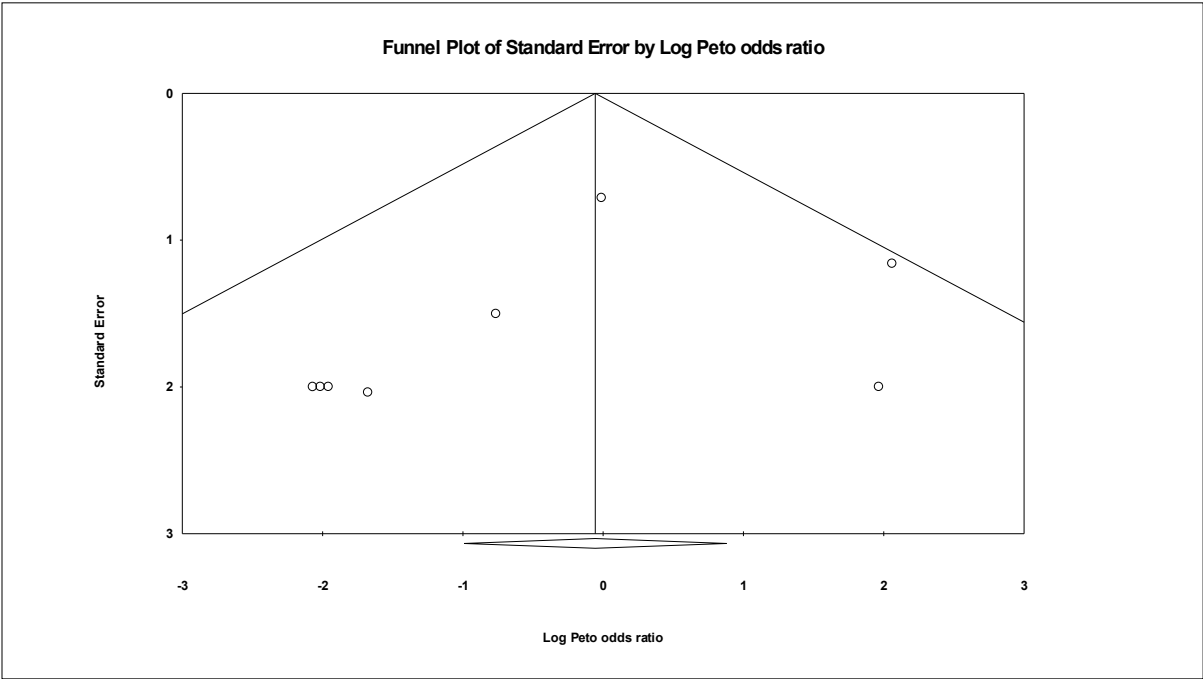
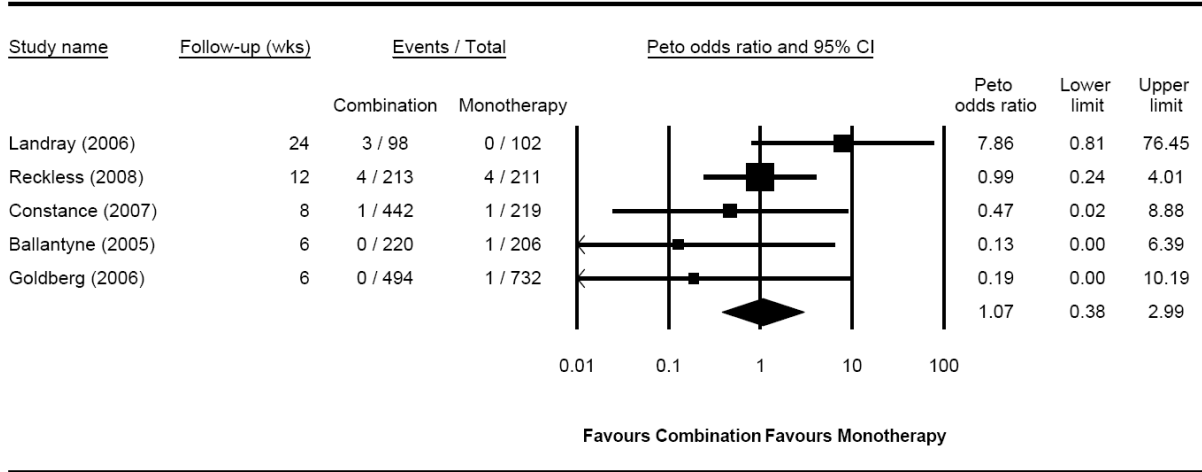


Figure G-2. Forest and funnel plots of all-cause mortality for ezetimibe plus statin therapy compared with statin monotherapy in all participants in trials with adequate allocation concealment



$I^2 = 22.13$

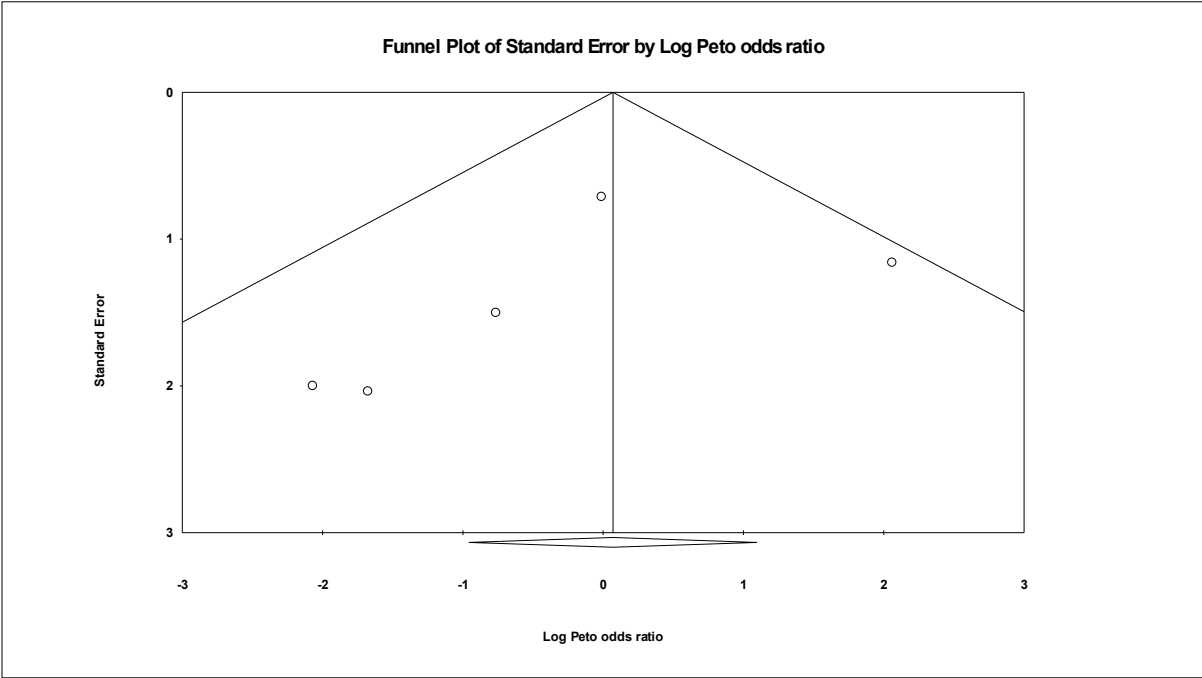
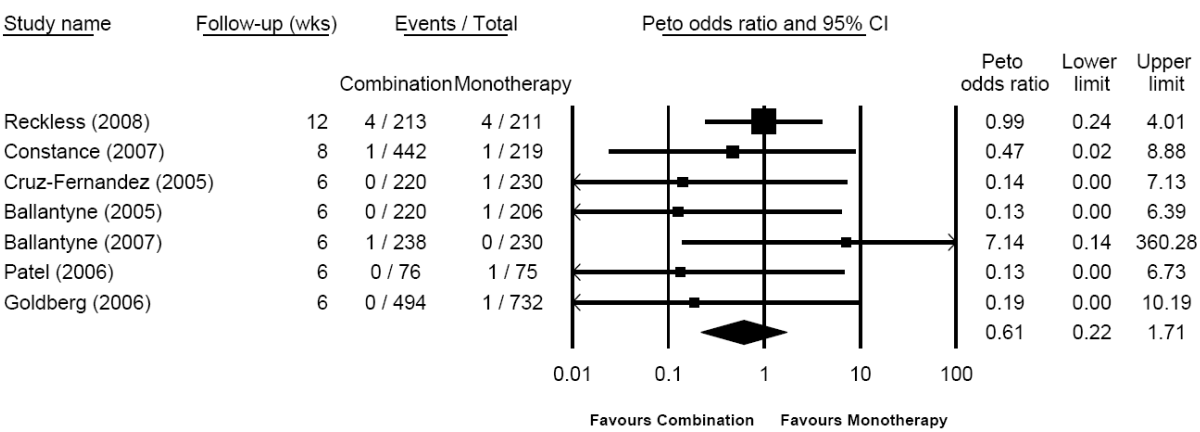


Figure G-3. Forest and funnel plots of all-cause mortality for ezetimibe plus statin therapy compared with statin monotherapy in participants requiring intensive lipid lowering therapy



$I^2 = 0$

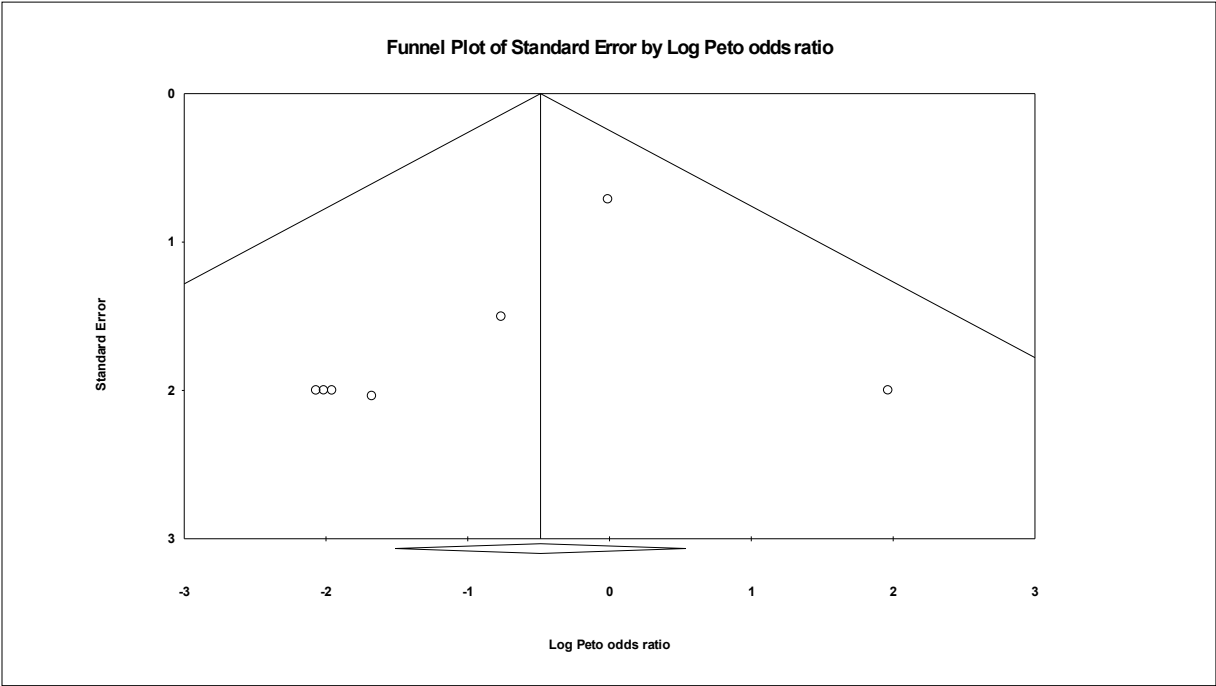
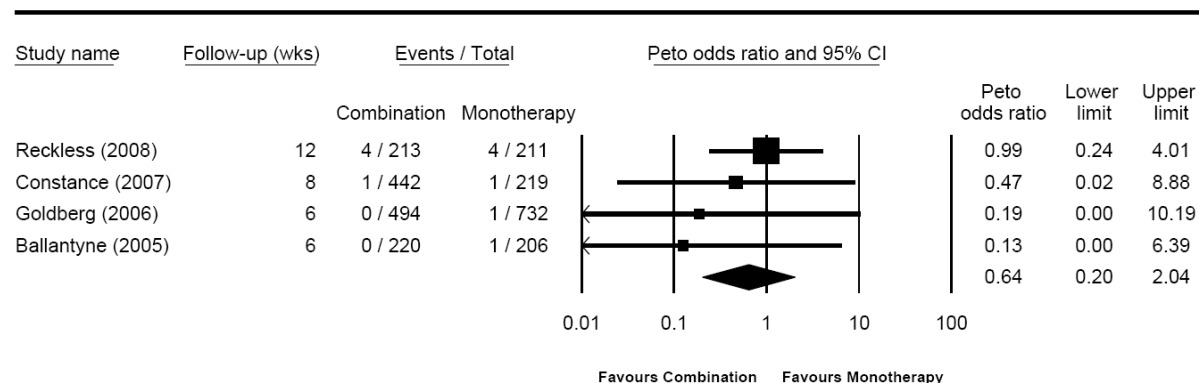
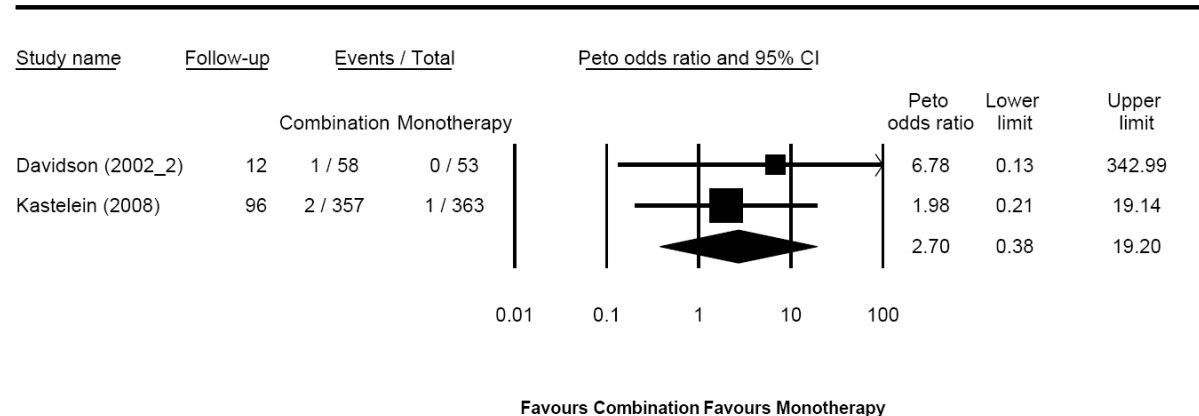


Figure 4. Forest plot of all-cause mortality for ezetimibe plus statin therapy compared with statin monotherapy in participants requiring intensive lipid lowering, trials with adequate allocation concealment



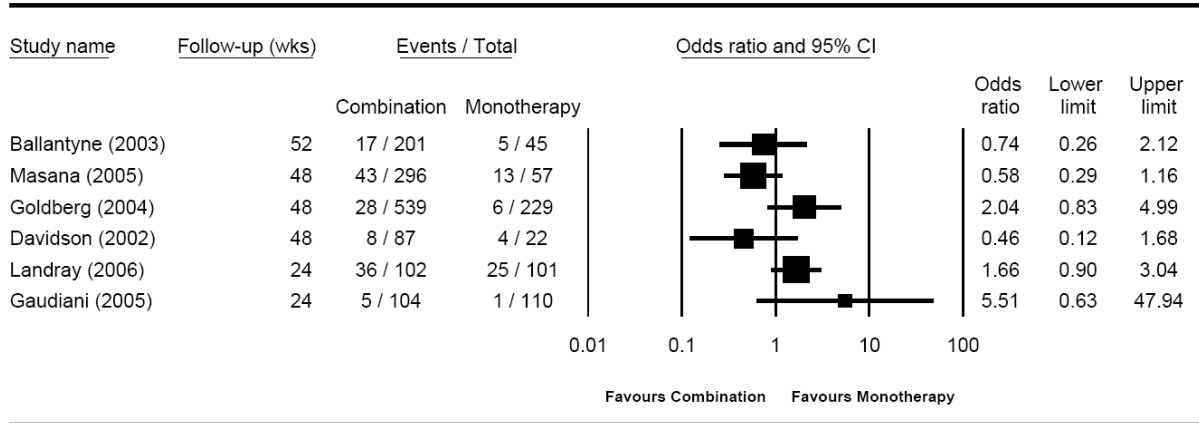
$I^2 = 0$

Figure G-5. Forest plot of vascular death for ezetimibe plus statin therapy compared with statin monotherapy in all participants



$I^2 = 0$

Figure G-6. Forest and funnel plots of serious adverse events for ezetimibe plus statin therapy compared with statin monotherapy in trials 24 weeks or more duration



$I^2 = 55.78$

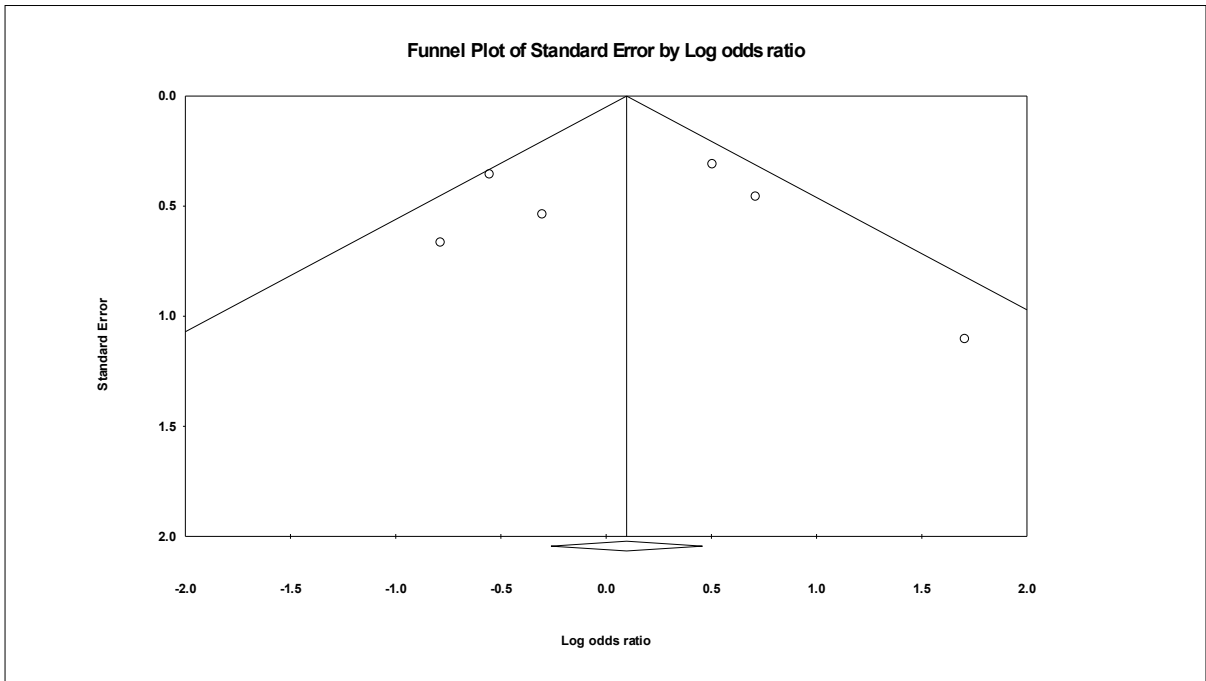
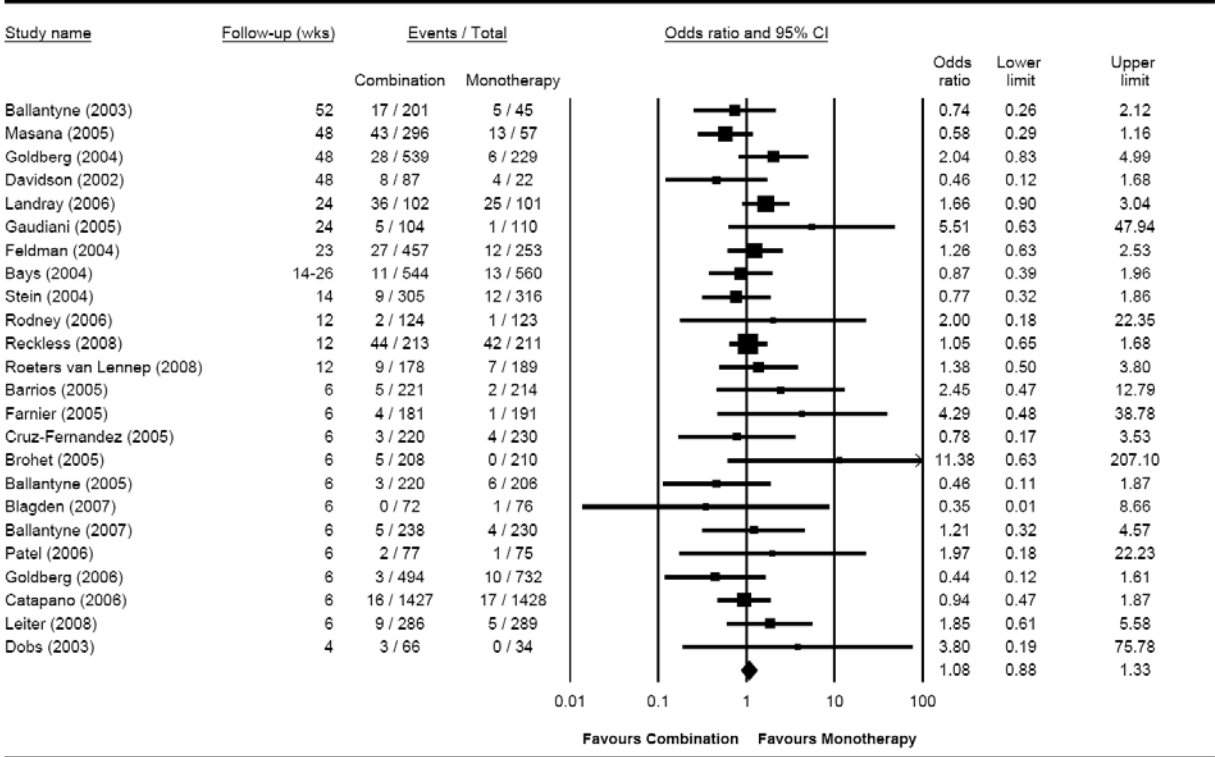


Figure G-7. Forest and funnel plots of serious adverse events for ezetimibe plus statin therapy compared with statin monotherapy in all participants



$I^2 = 3.21$

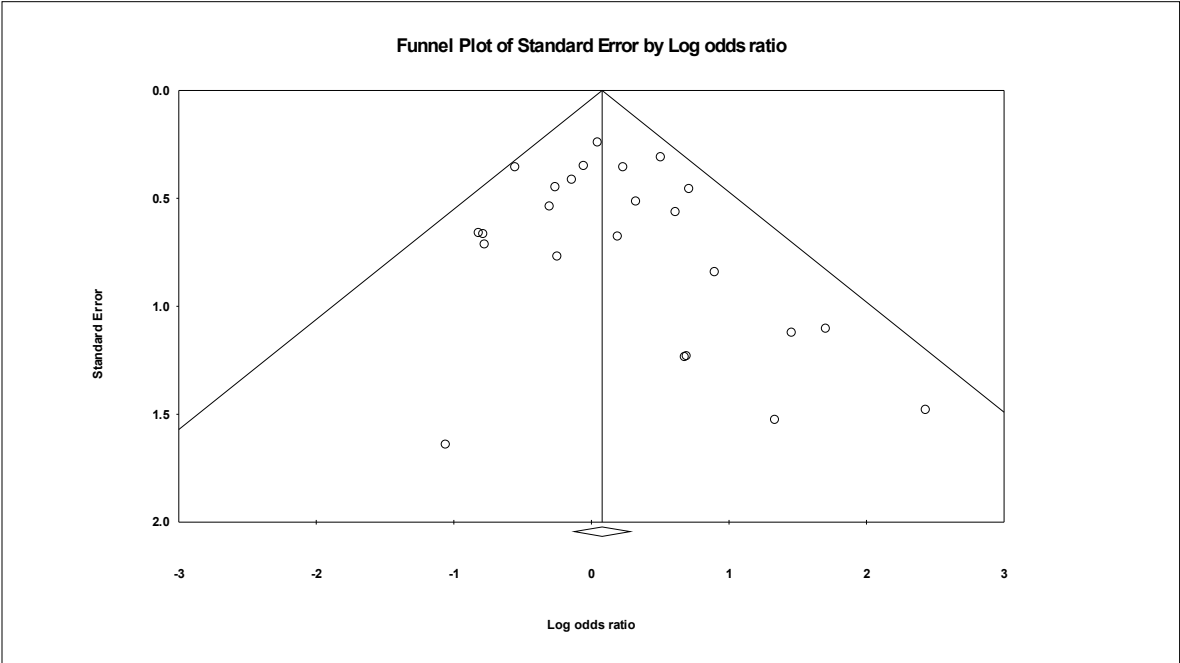


Figure G-7 continued: Funnel plot of trials with followup longer than 6 months

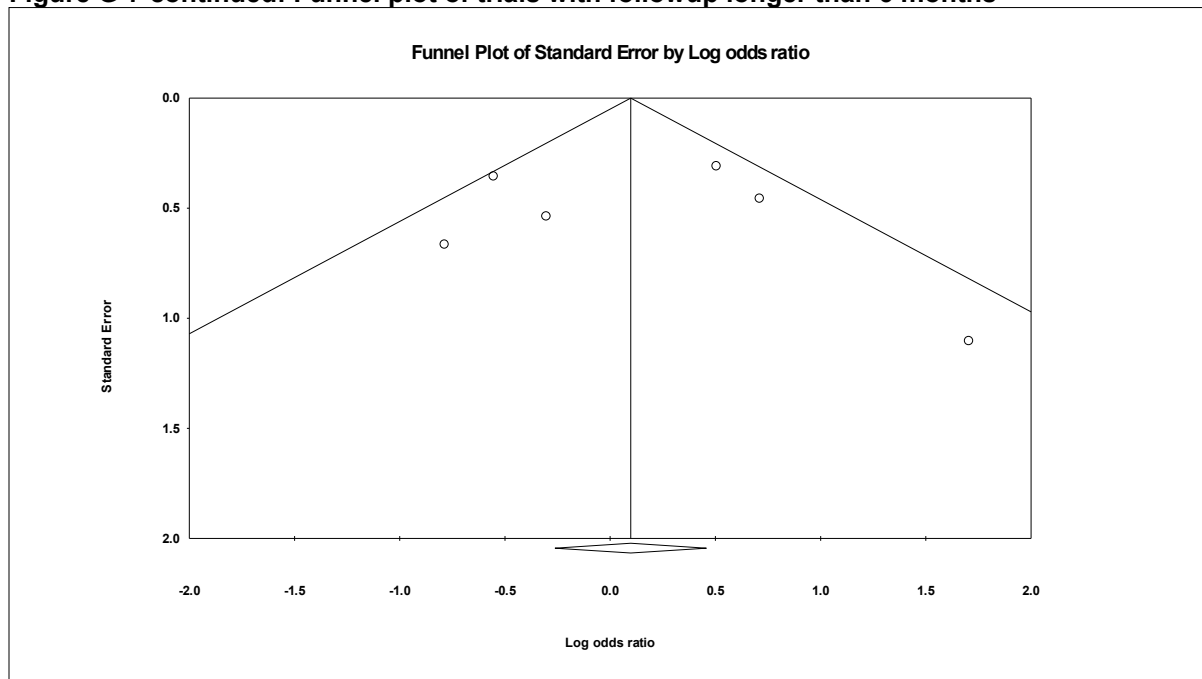
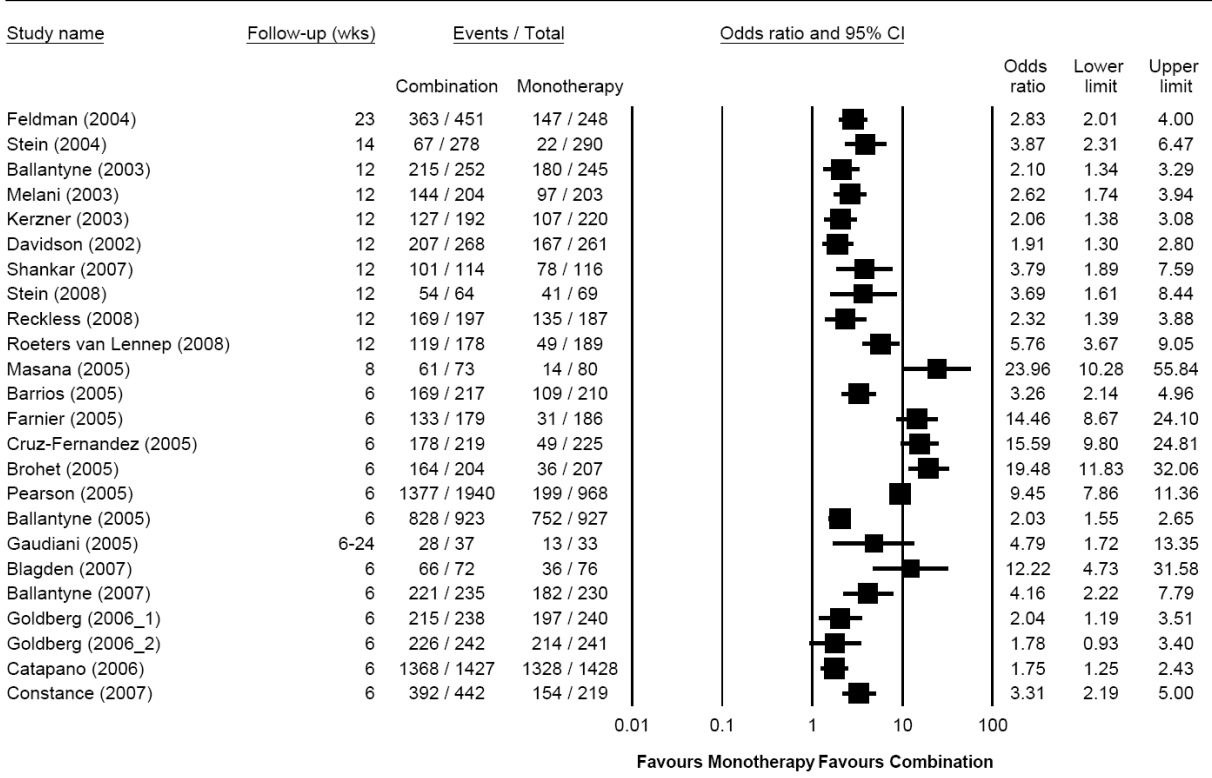


Figure G-8. Forest and funnel plots of participants attaining ATP III LDL-c targets for ezetimibe plus statin therapy compared with statin monotherapy in all participants



$I^2 = 92.63$

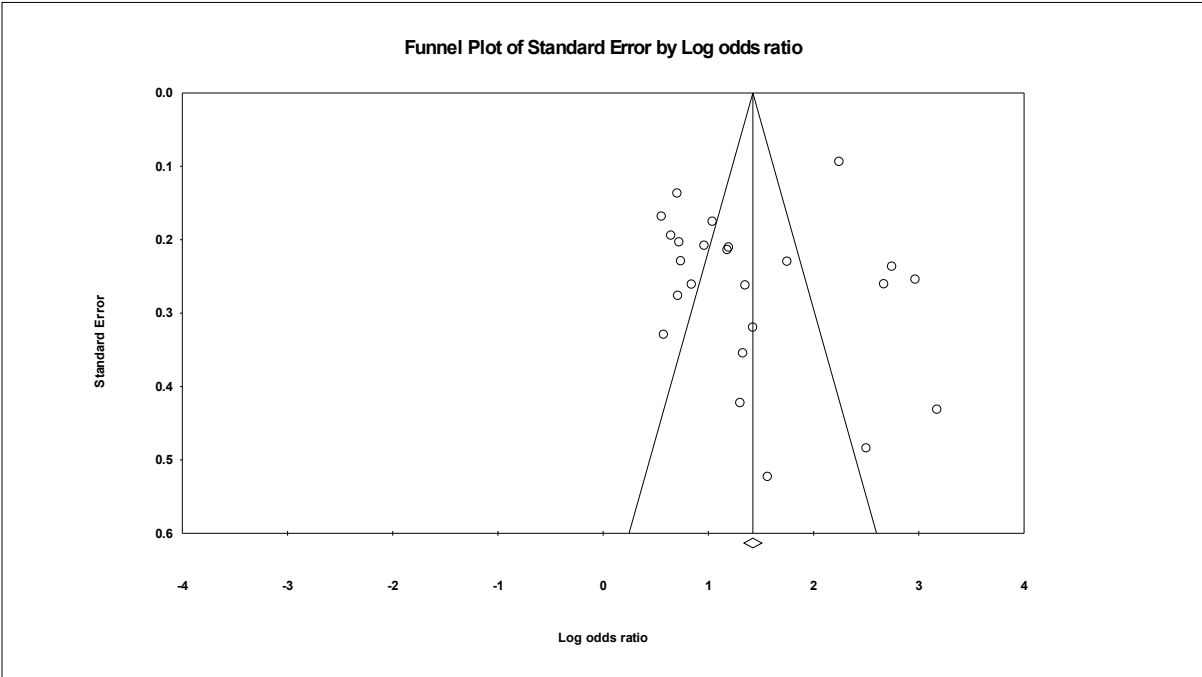
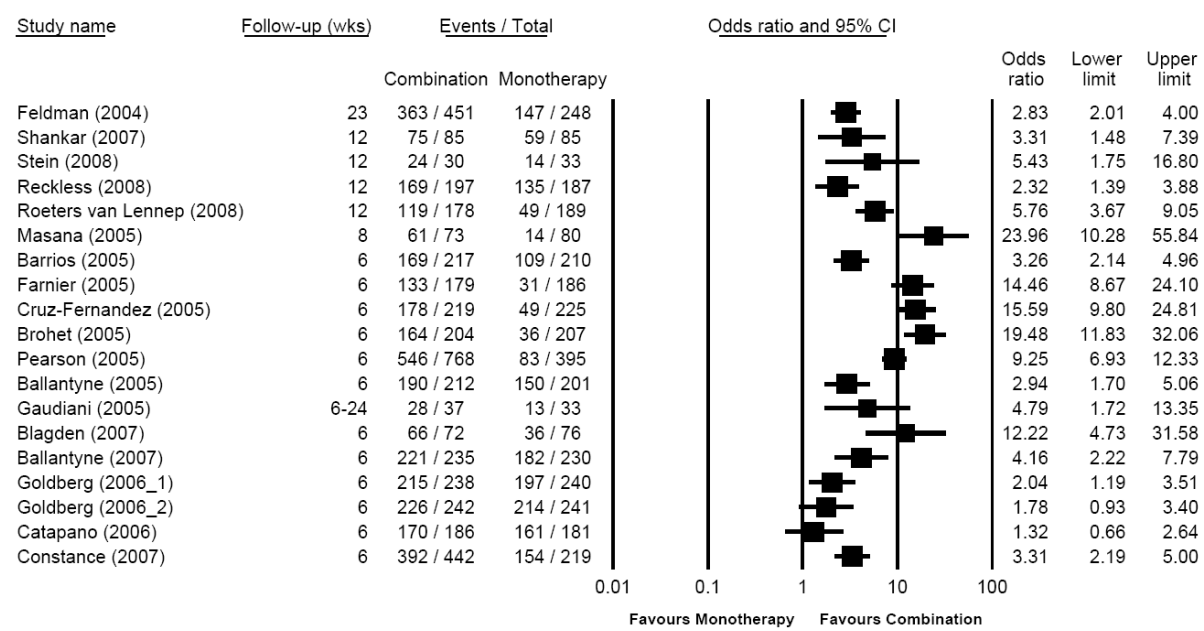


Figure G-9. Forest and funnel plots of participants attaining ATP III LDL-c targets for ezetimibe plus statin therapy compared with statin monotherapy, in participants requiring intensive lipid lowering therapy



$I^2 = 89$

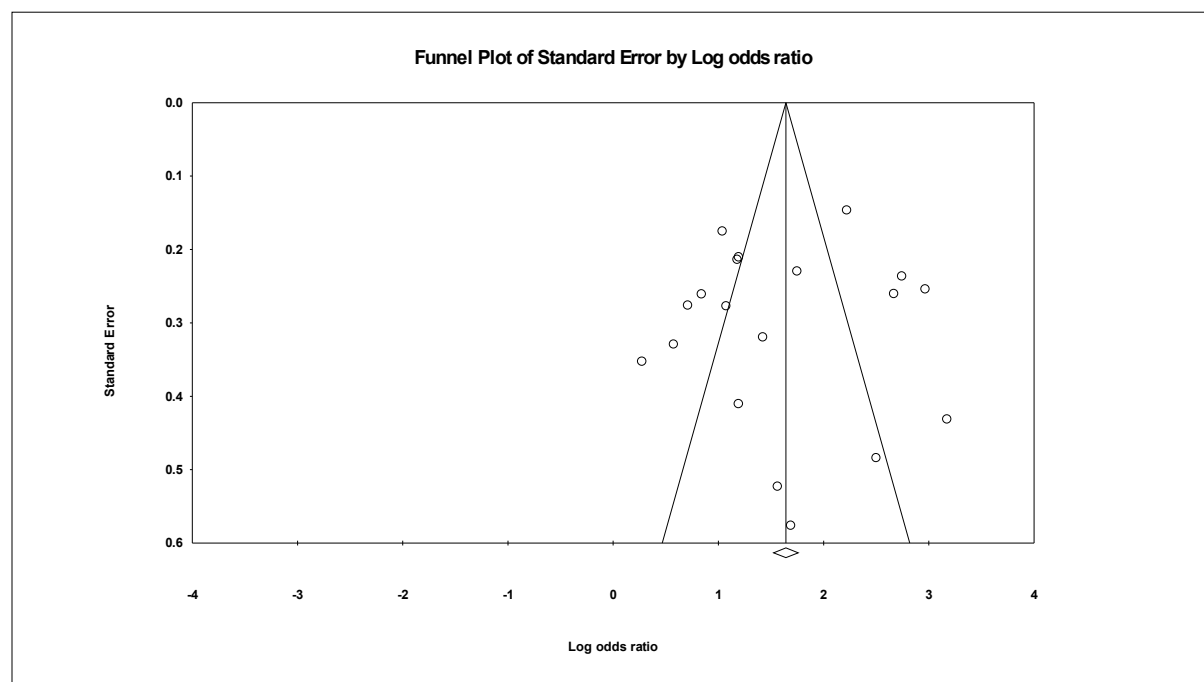
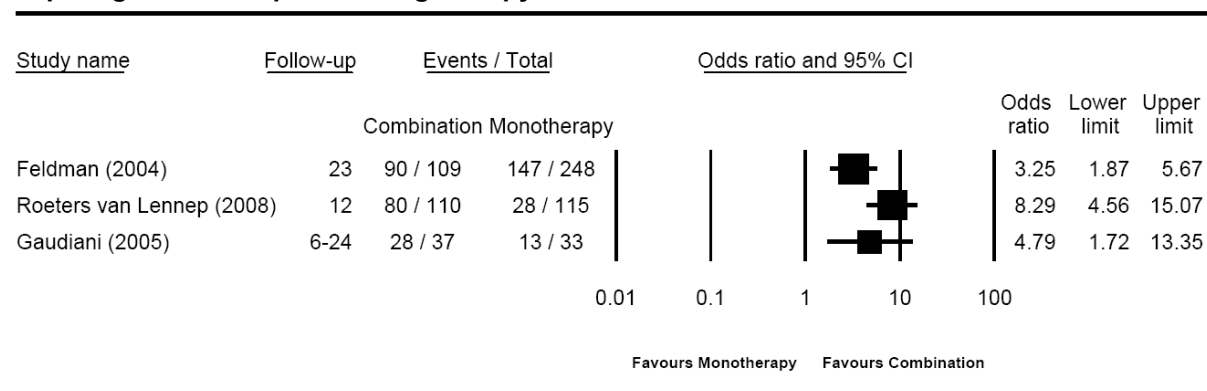
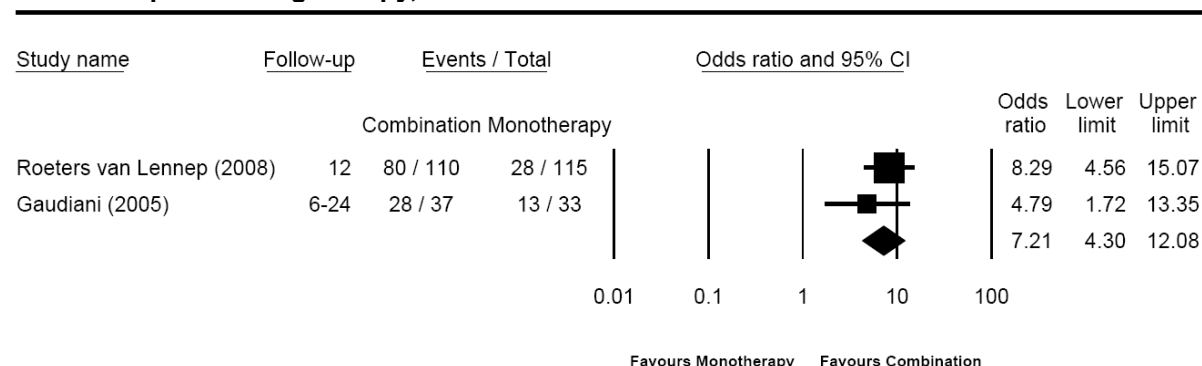


Figure G-10. Forest plot of achievement of ATP III LDL-c targets for lower dose ezetimibe plus simvastatin therapy compared with higher dose simvastatin monotherapy, in participants requiring intensive lipid lowering therapy



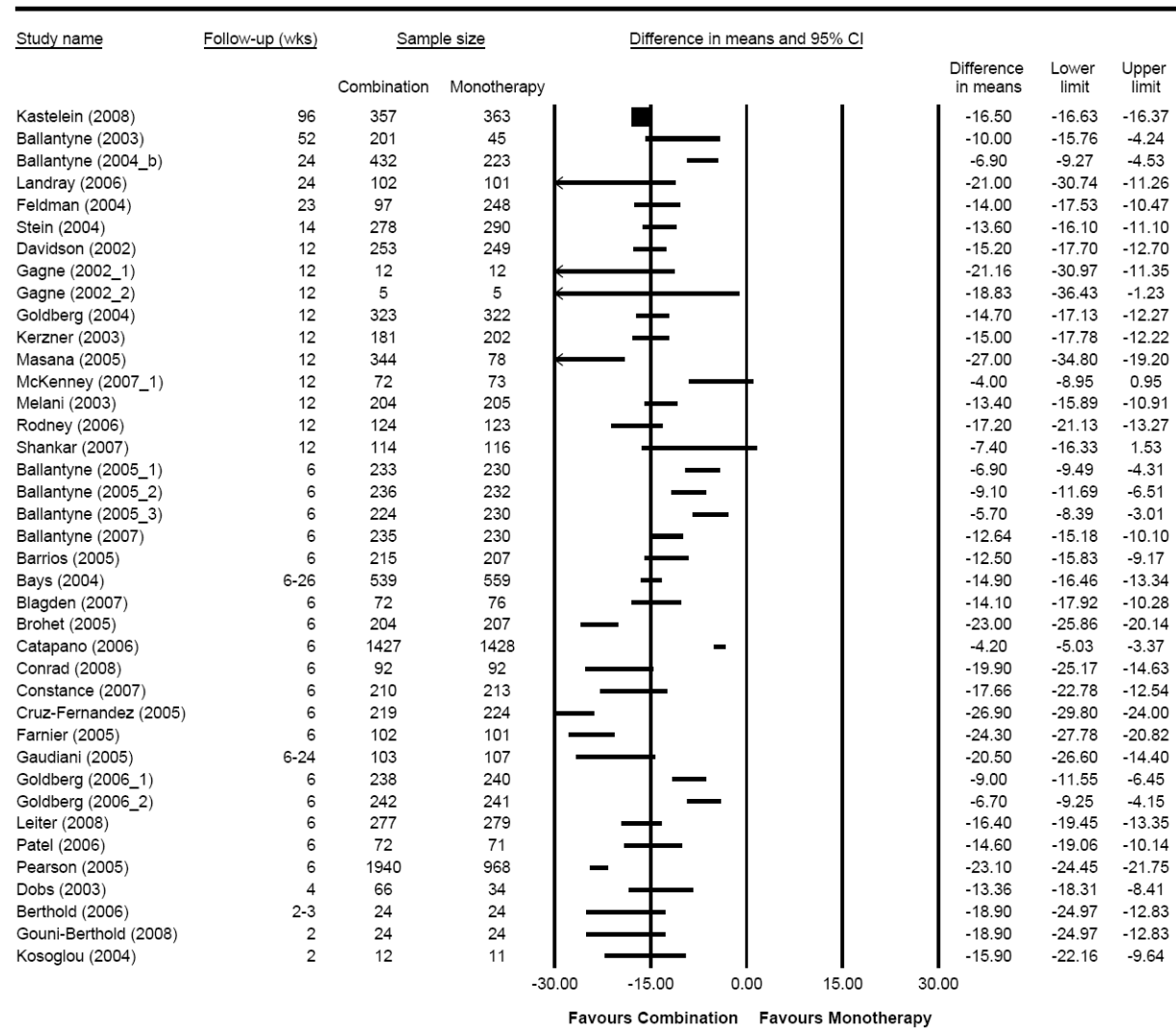
$I^2 = 60.32$

Figure G-11. Forest plot of achievement of ATP III LDL-c targets for lower dose ezetimibe plus simvastatin therapy compared with higher dose simvastatin monotherapy in participants requiring intensive lipid lowering therapy, in studies with fixed doses or fixed titration of doses



$I^2 = 0$

Figure G-12. Forest and funnel plots of LDL-c difference in mean percentage change from baseline for ezetimibe plus statin therapy compared with statin monotherapy in all participants



$I^2 = 97.23$

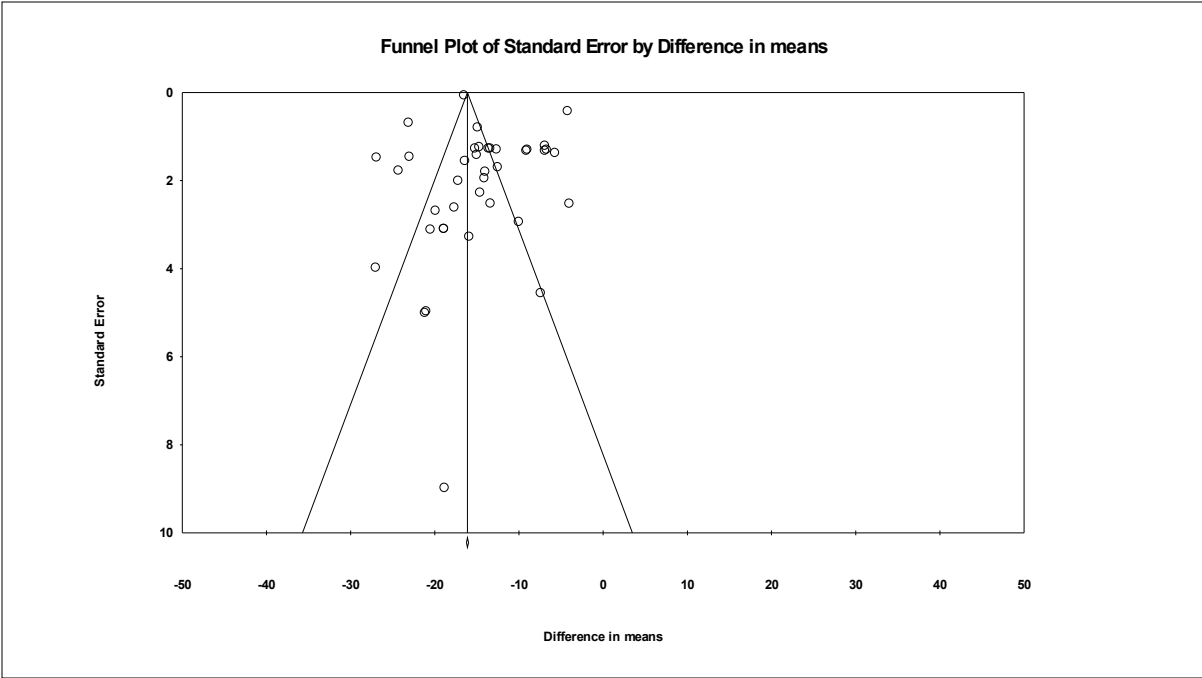


Figure G-13. Forest and funnel plots of LDL-c difference in mean percentage change from baseline for ezetimibe plus lower dose simvastatin therapy compared with higher dose simvastatin monotherapy in all participants

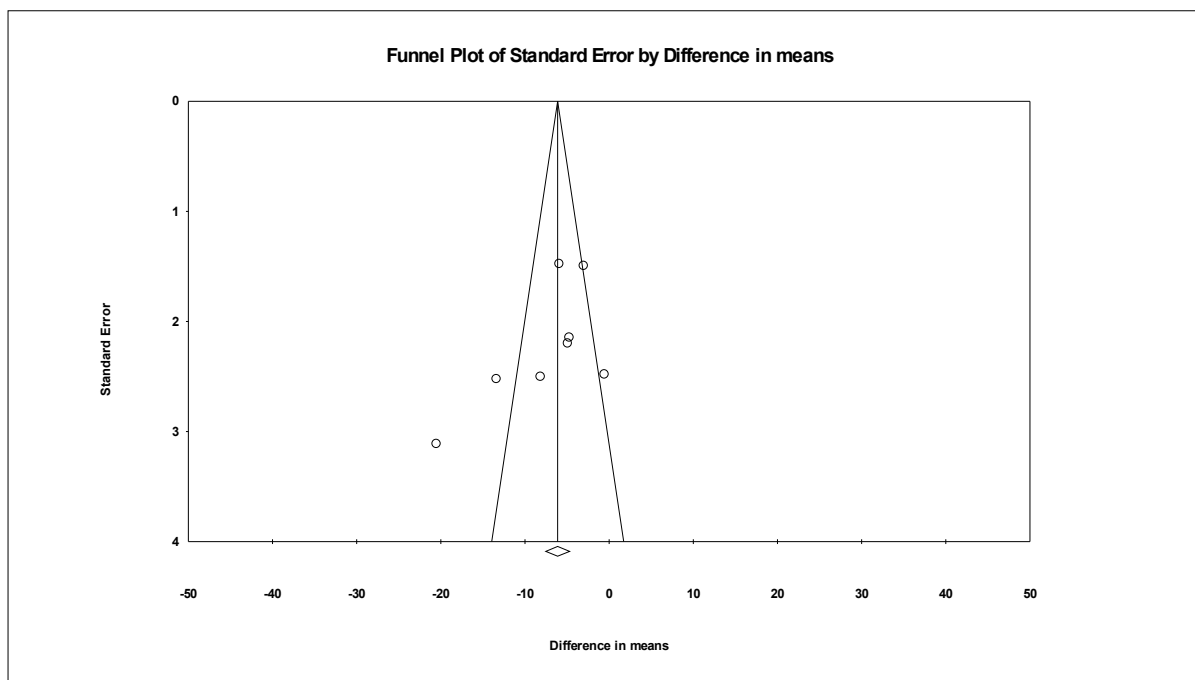
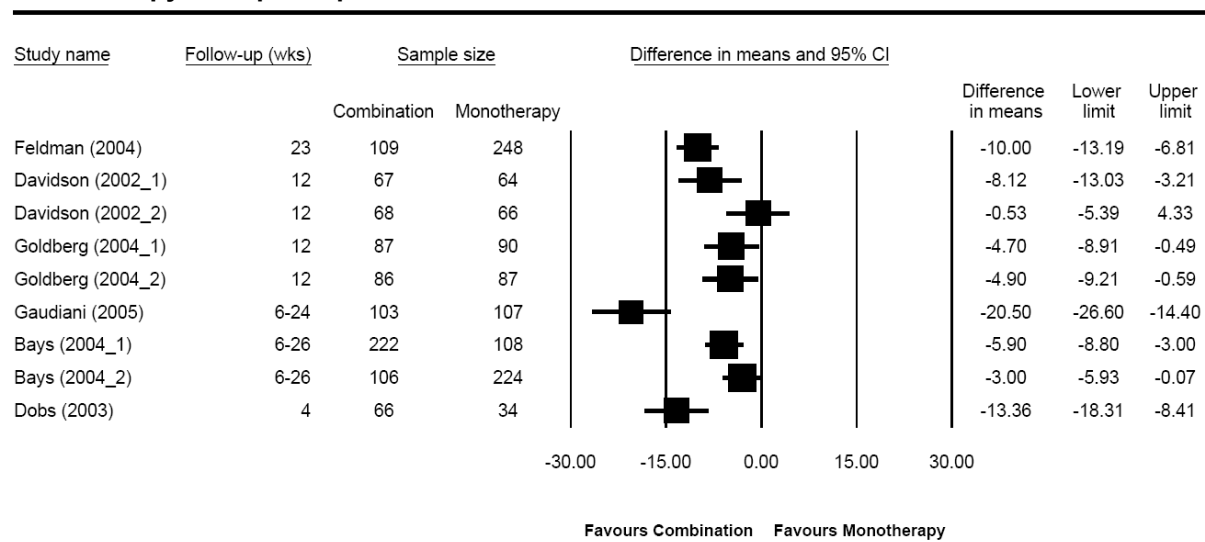
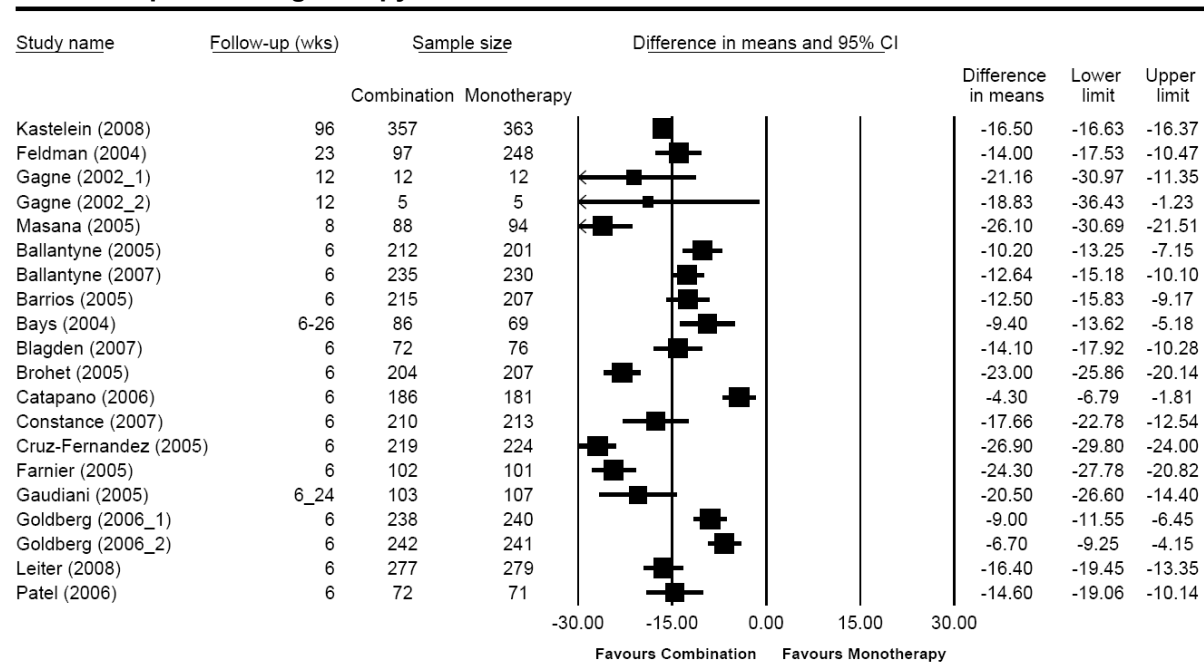


Figure G-14. Forest and funnel plots of LDL-c difference in mean percentage change from baseline for ezetimibe plus statin therapy compared with statin monotherapy in participants requiring intensive lipid lowering therapy



$I^2 = 94.33$

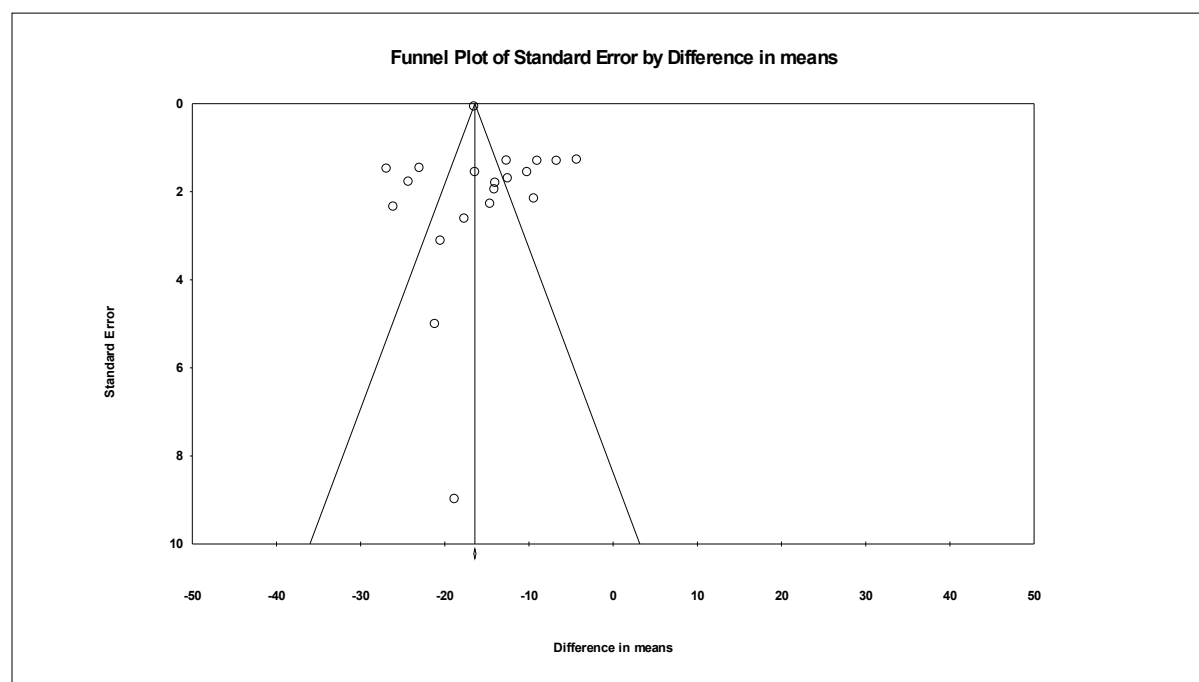
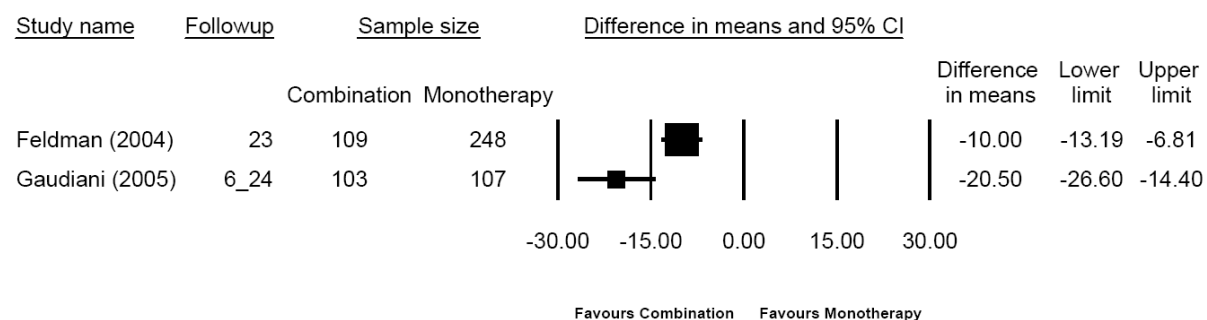


Figure G-15. Forest and funnel plots of LDL-c difference in mean percentage change from baseline for ezetimibe plus lower dose simvastatin therapy compared with higher dose simvastatin monotherapy in participants requiring intensive lipid lowering therapy



$I^2 = 88.80$

Figure G-16. Funnel plot of HDL-c difference in mean percentage change from baseline for ezetimibe plus statin therapy compared with statin monotherapy in all participants

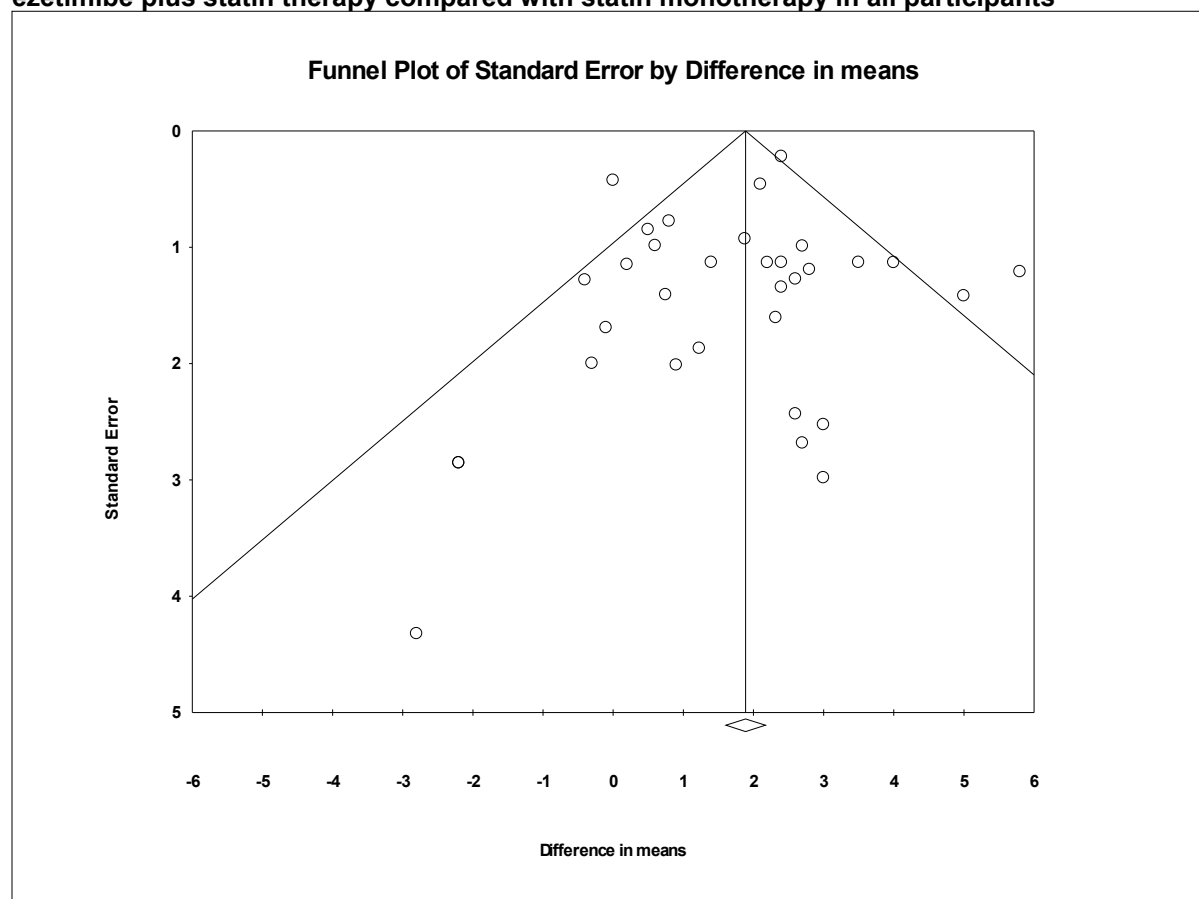


Figure G-17. Funnel plot of HDL-c difference in mean percentage change from baseline for ezetimibe plus lower dose simvastatin therapy compared with higher simvastatin monotherapy in all participants, in trials with fixed doses or fixed titration of doses

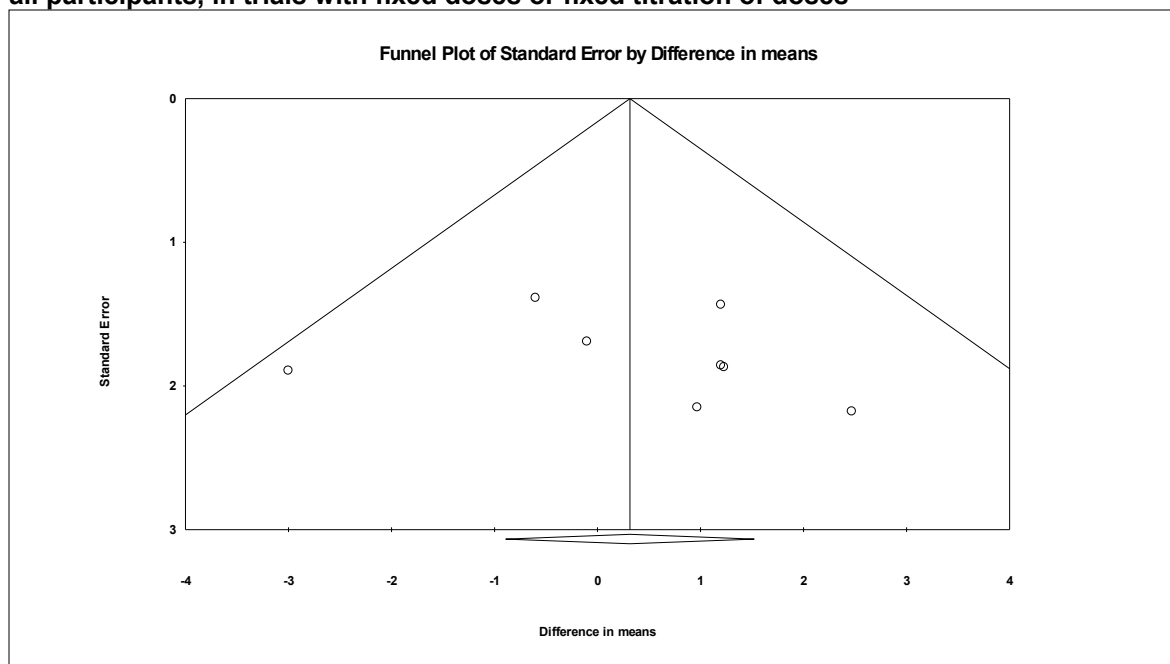


Figure G-18. Funnel plot of HDL-c difference in mean percentage change from baseline for ezetimibe plus statin therapy compared with statin monotherapy in participants requiring intensive lipid lowering

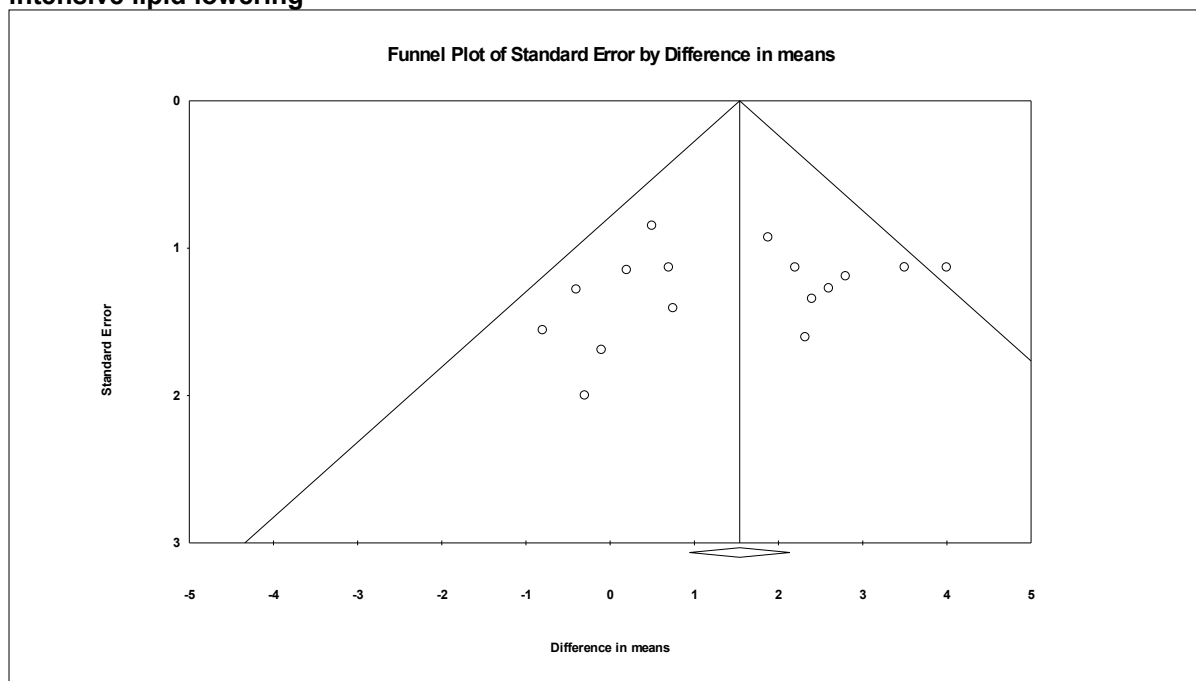


Figure G-19. Funnel plot of difference in total cholesterol:HDL-c ratio percentage change from baseline for ezetimibe plus statin therapy compared with statin monotherapy in all participants

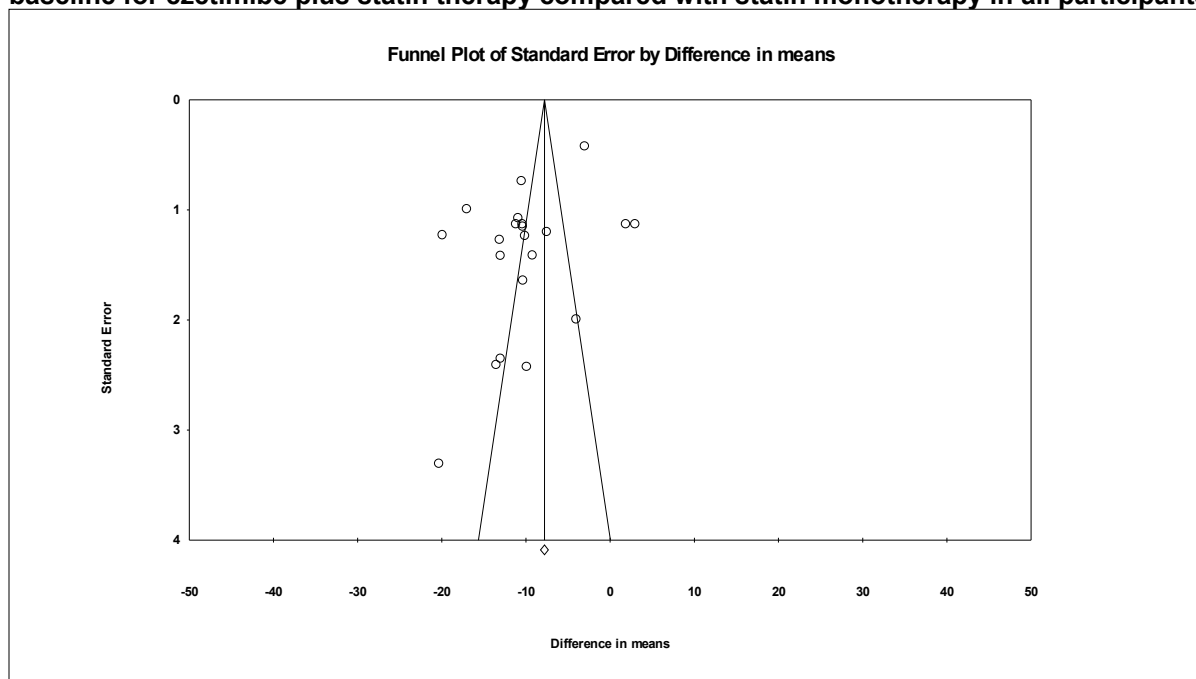


Figure G-20. Funnel plot of total cholesterol:HDL-c ratio difference in mean percentage change from baseline for ezetimibe plus lower dose simvastatin therapy compared with higher simvastatin monotherapy in all participants, in studies with fixed doses or fixed titration of doses

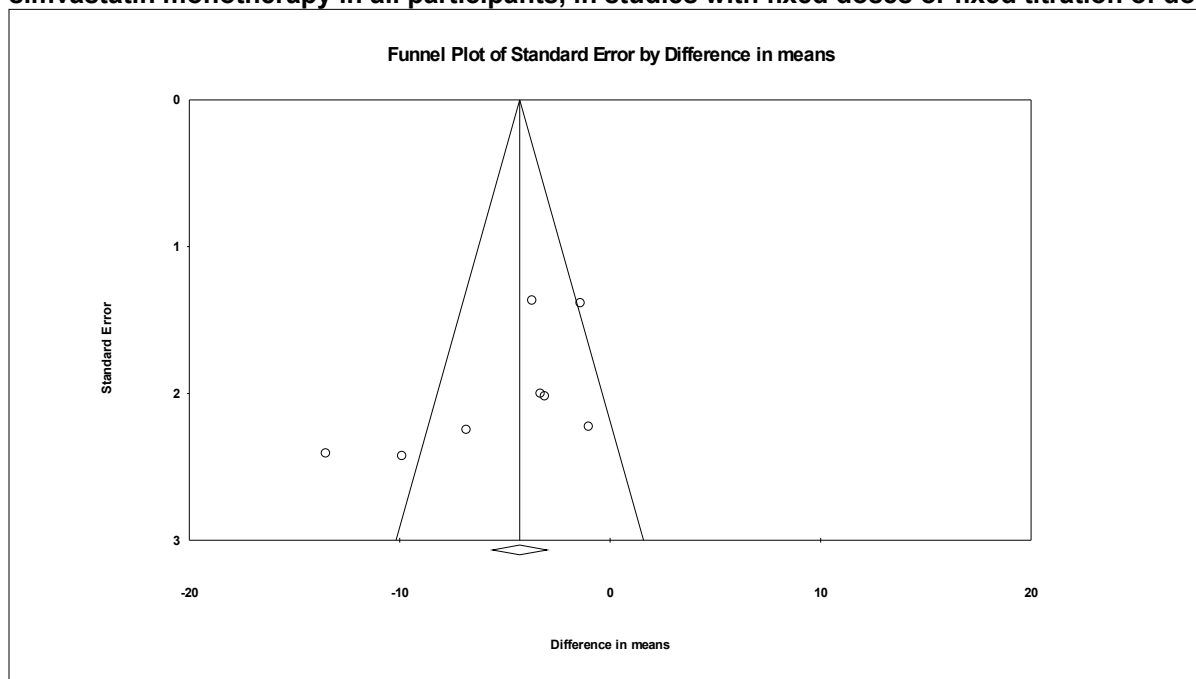


Figure G-21. Funnel plots of total cholesterol:HDL-c (ratio) difference in mean percentage change from baseline for ezetimibe plus statin compared with statin monotherapy in participants requiring intensive lipid lowering therapy

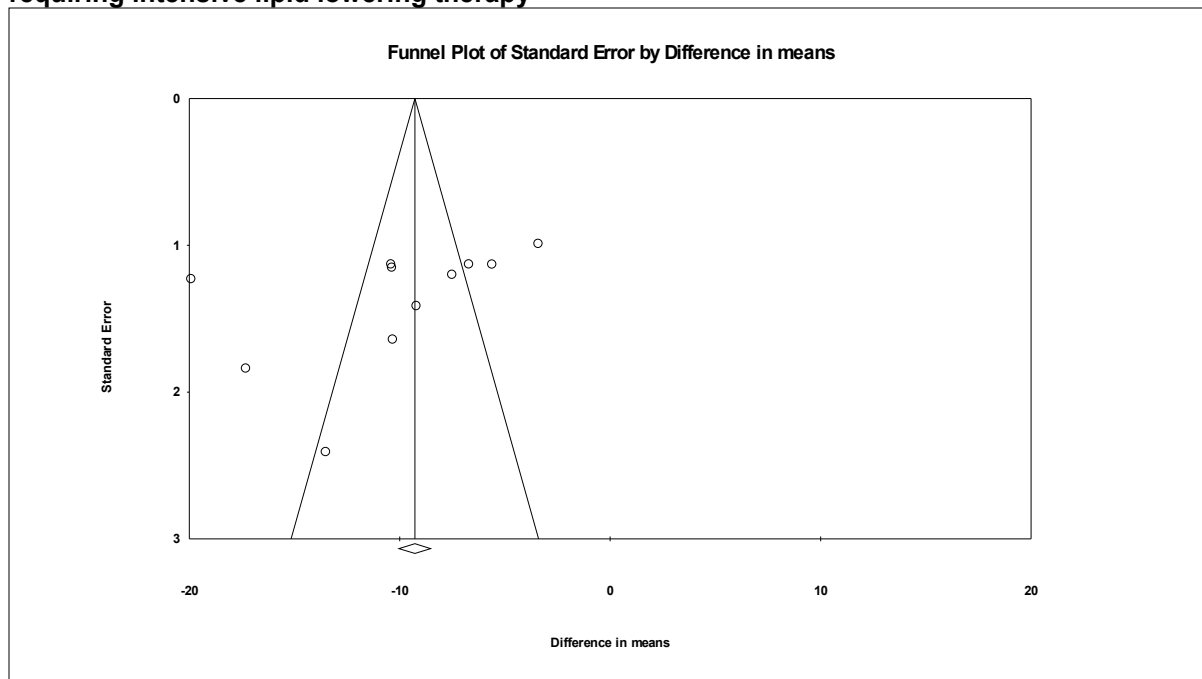


Figure G-22. Funnel plot of treatment adherence, for ezetimibe plus statin therapy compared with statin monotherapy in all participants

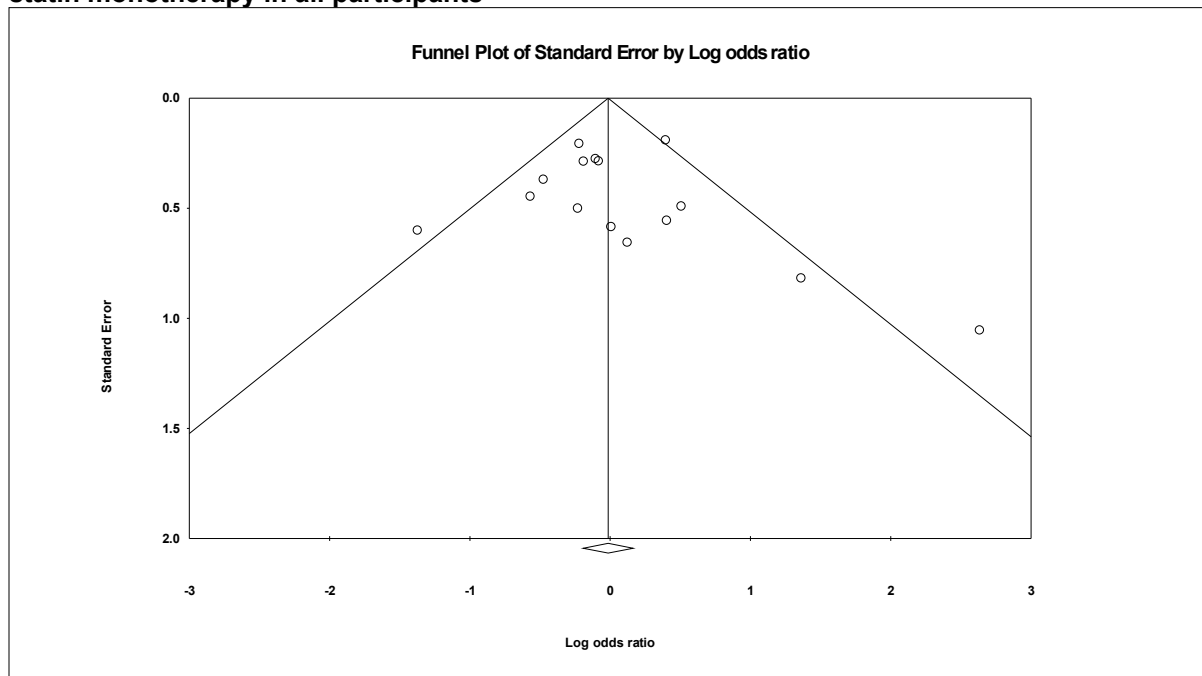


Figure G-23. Funnel plot of proportion of participants with at least one adverse event, for ezetimibe plus statin therapy compared with statin monotherapy in all participants

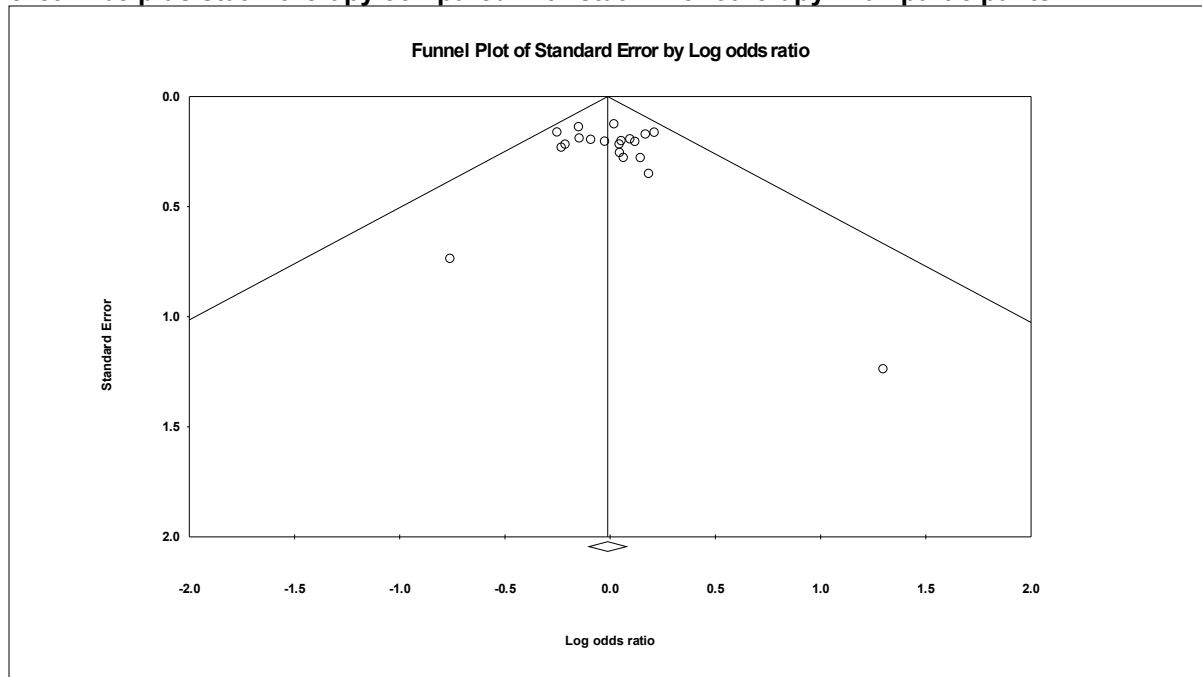


Figure G-24. Funnel plot of proportion of participants withdrawing from treatment due to an adverse event, for ezetimibe plus statin therapy compared with statin monotherapy in all participants

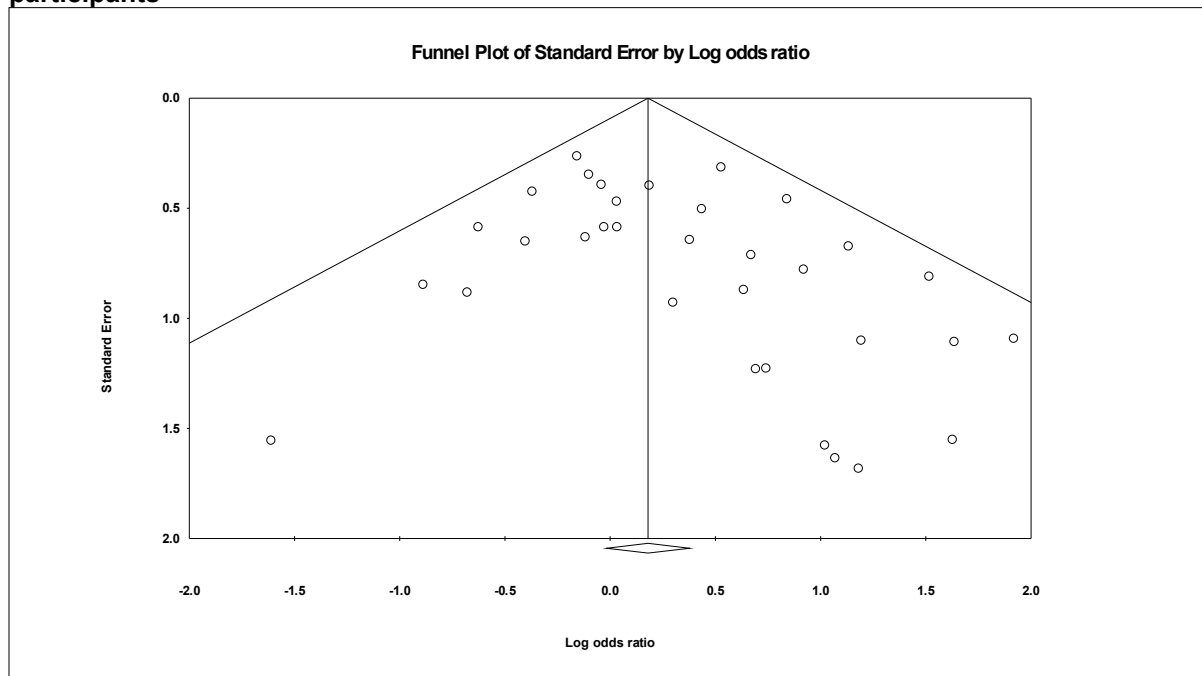


Figure G-25. Funnel plot of proportion of participants with AST and/or ALT above 3 times the upper limit of normal, and/or hepatitis, for ezetimibe plus statin therapy compared with statin monotherapy in all participants

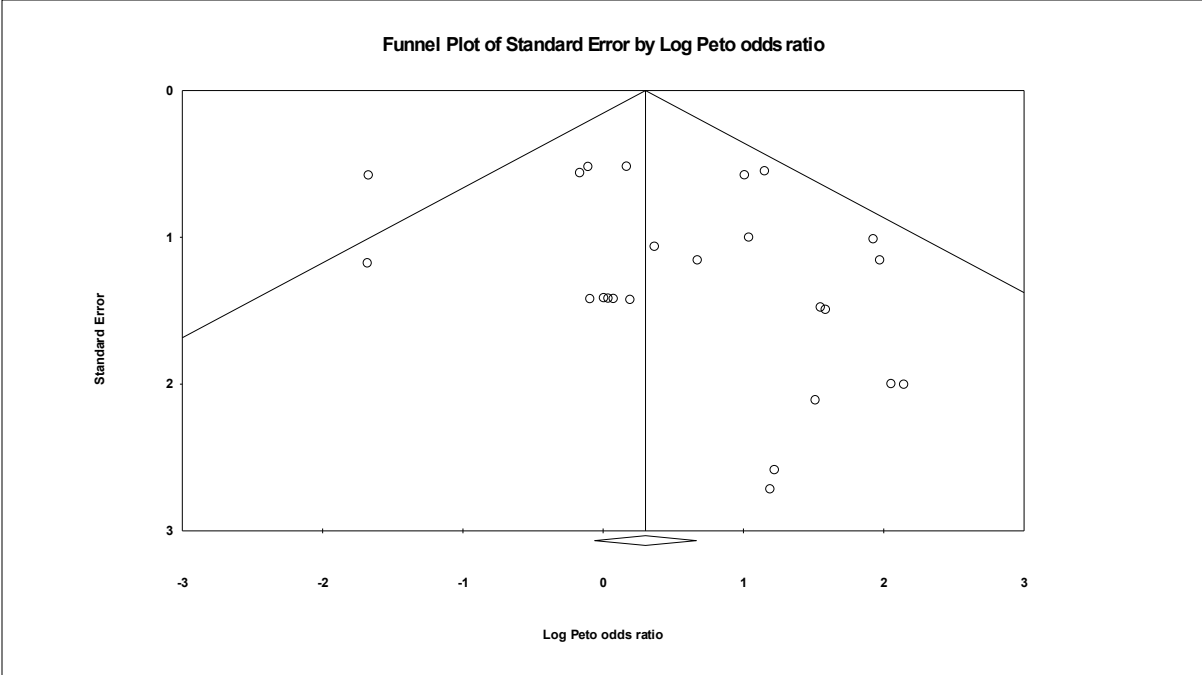


Figure G-26. Funnel plot of proportion of participants with AST and/or ALT above 3 times the upper limit of normal, and/or hepatitis, for ezetimibe plus lower dose simvastatin therapy compared with higher dose simvastatin monotherapy in all participants

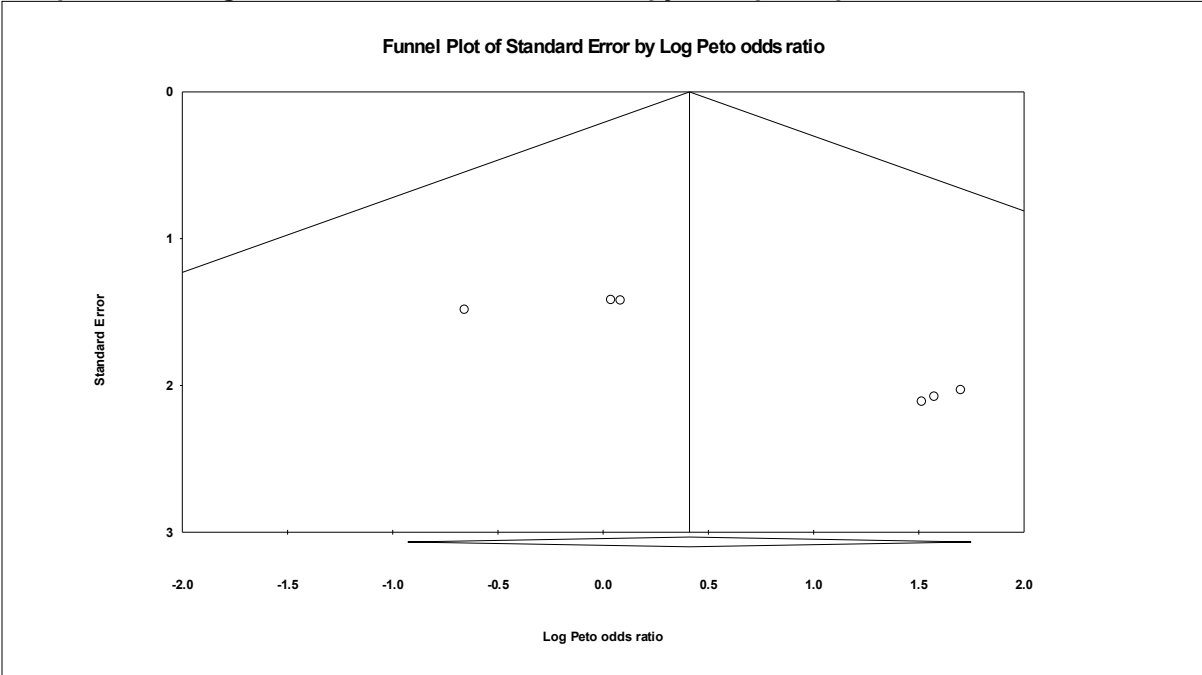


Figure G-27. Funnel plot of proportion of participants with AST and/or ALT above 3 times the upper limit of normal, and/or hepatitis, for ezetimibe plus lower dose simvastatin therapy compared with higher dose simvastatin monotherapy in all participants, in studies with fixed doses or fixed titration of doses

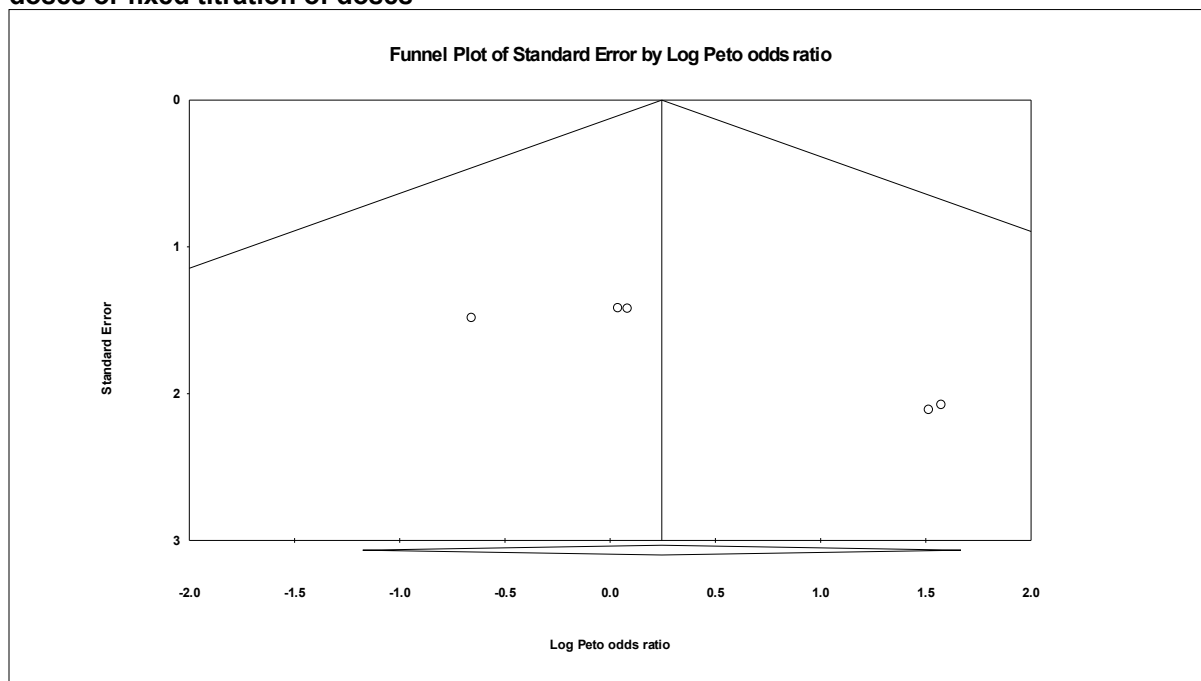


Figure G-28. Funnel plot of proportion of participants experiencing myalgia, for ezetimibe plus statin therapy compared with statin monotherapy in all participants

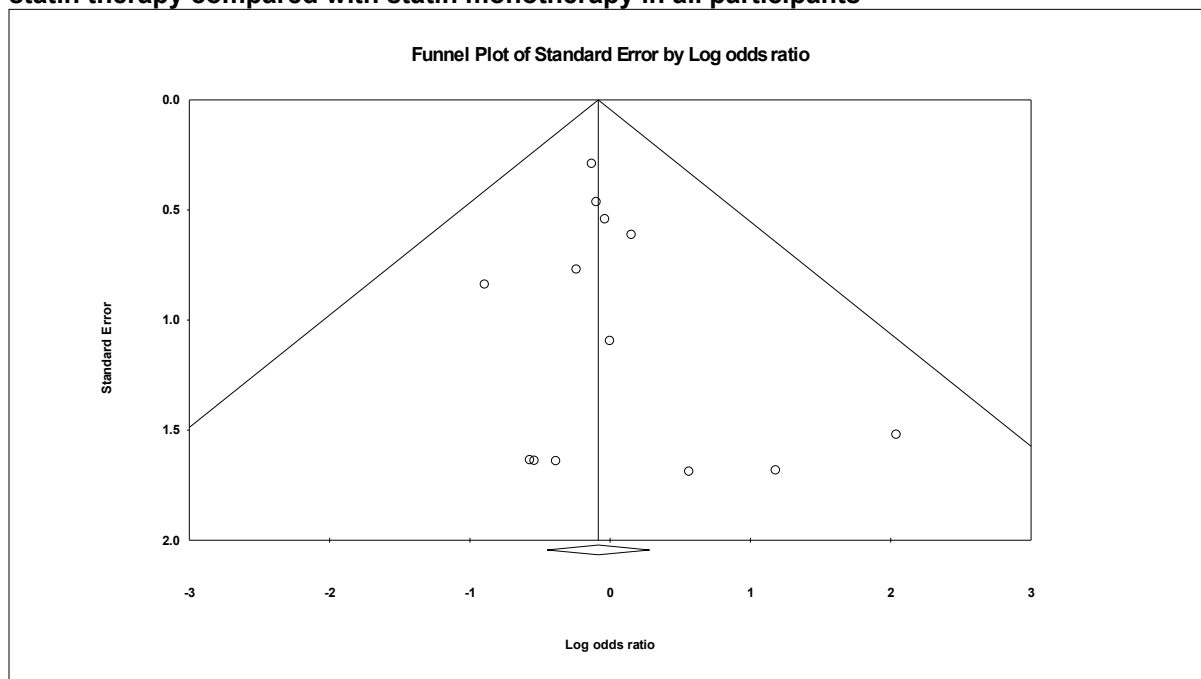


Figure G-29. Funnel plot of proportion of participants with CPK above 10 times the upper limit of normal, for ezetimibe plus statin therapy compared with statin monotherapy in all participants

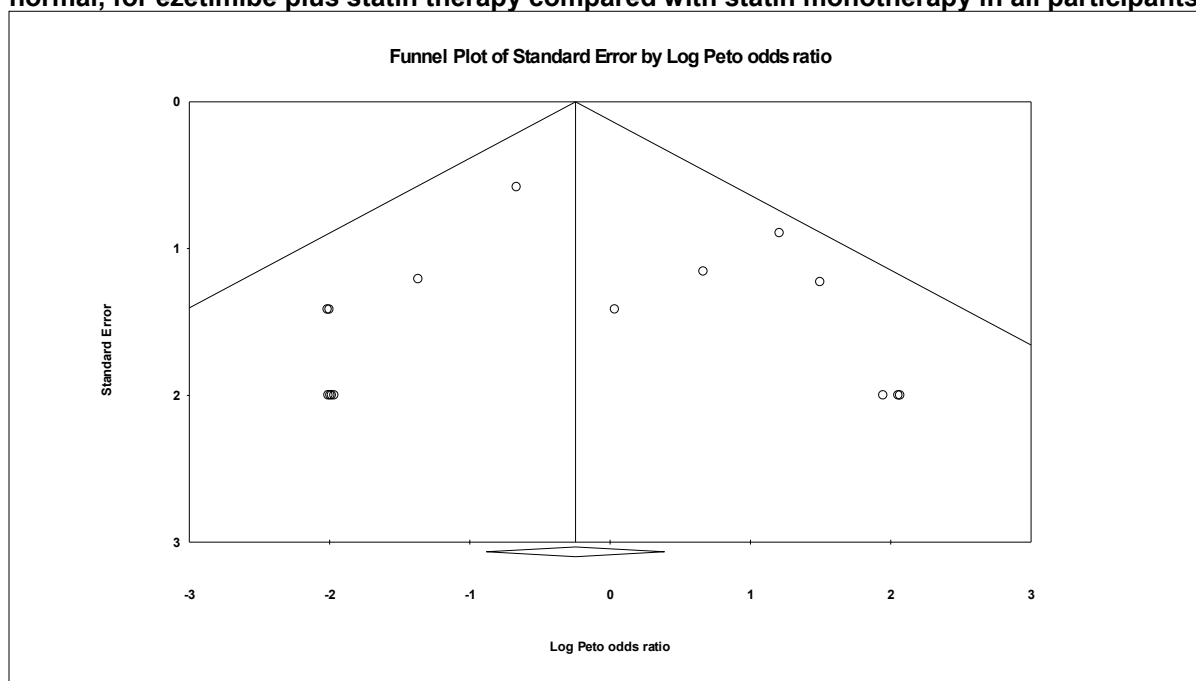
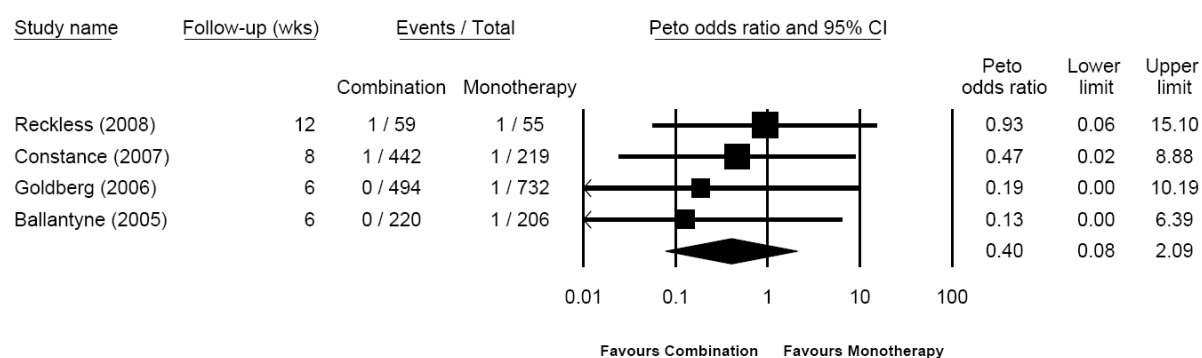
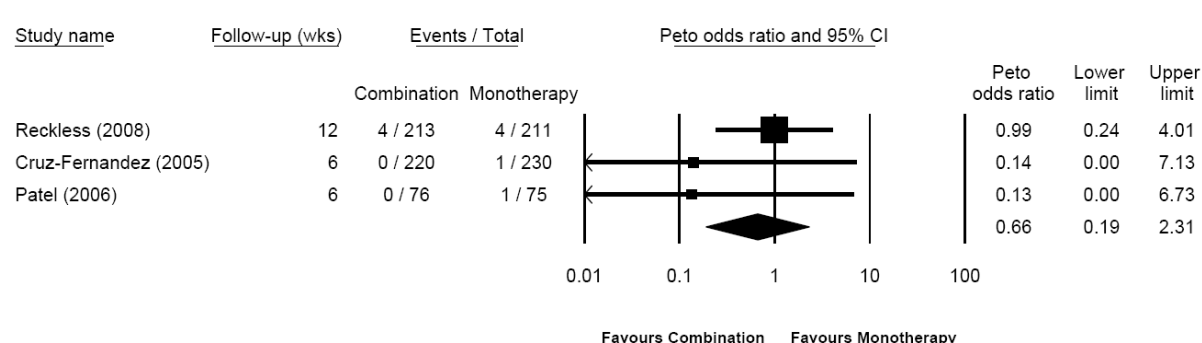


Figure G-30. Forest plot of all-cause mortality for ezetimibe plus statin therapy compared with statin monotherapy in participants with diabetes mellitus



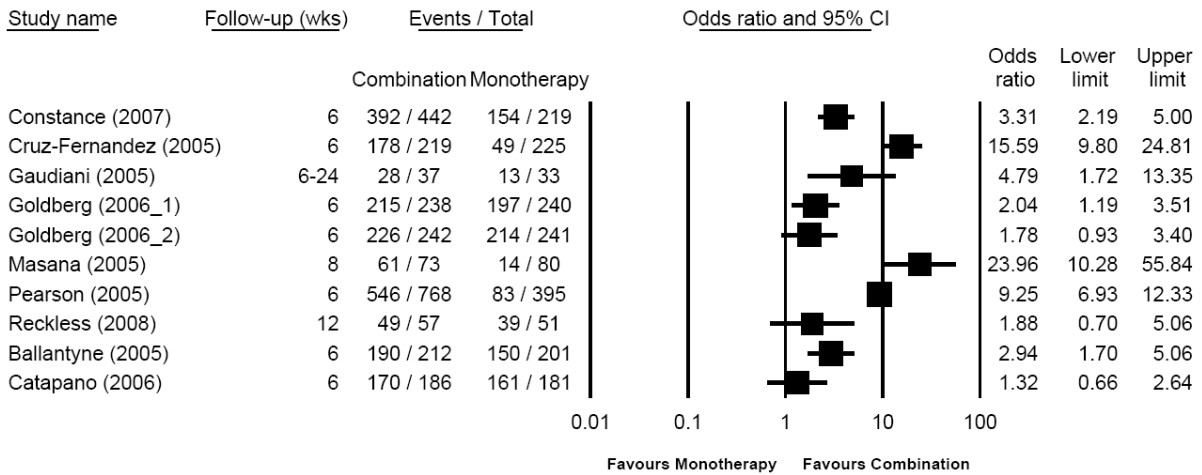
$I^2 = 0$

Figure G-31. Forest plot of all-cause mortality for ezetimibe plus statin therapy compared with statin monotherapy in participants with established vascular disease



$I^2 = 0$

Figure G-32. Forest and funnel plots of achievement of ATP III LDL-c targets for ezetimibe plus statin therapy compared with statin monotherapy in participants with diabetes mellitus



$I^2 = 90.94$

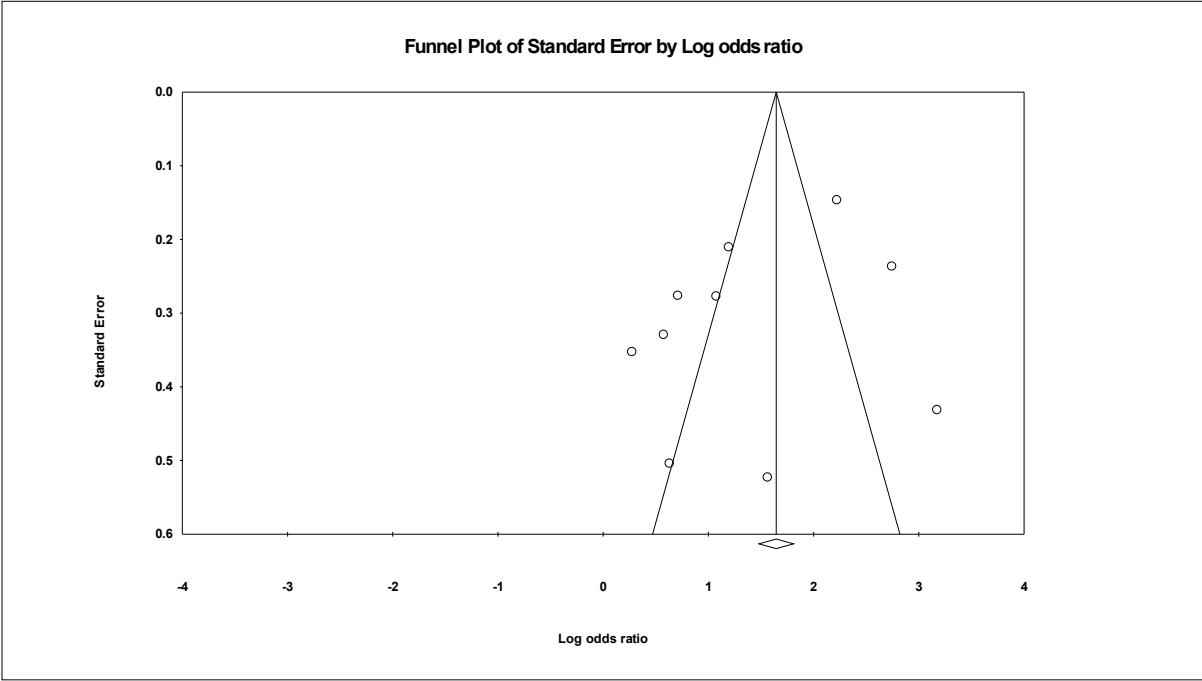


Figure G-33. Forest and funnel plots of achievement of ATP III LDL-c targets for ezetimibe plus statin therapy compared with statin monotherapy in participants with established vascular disease

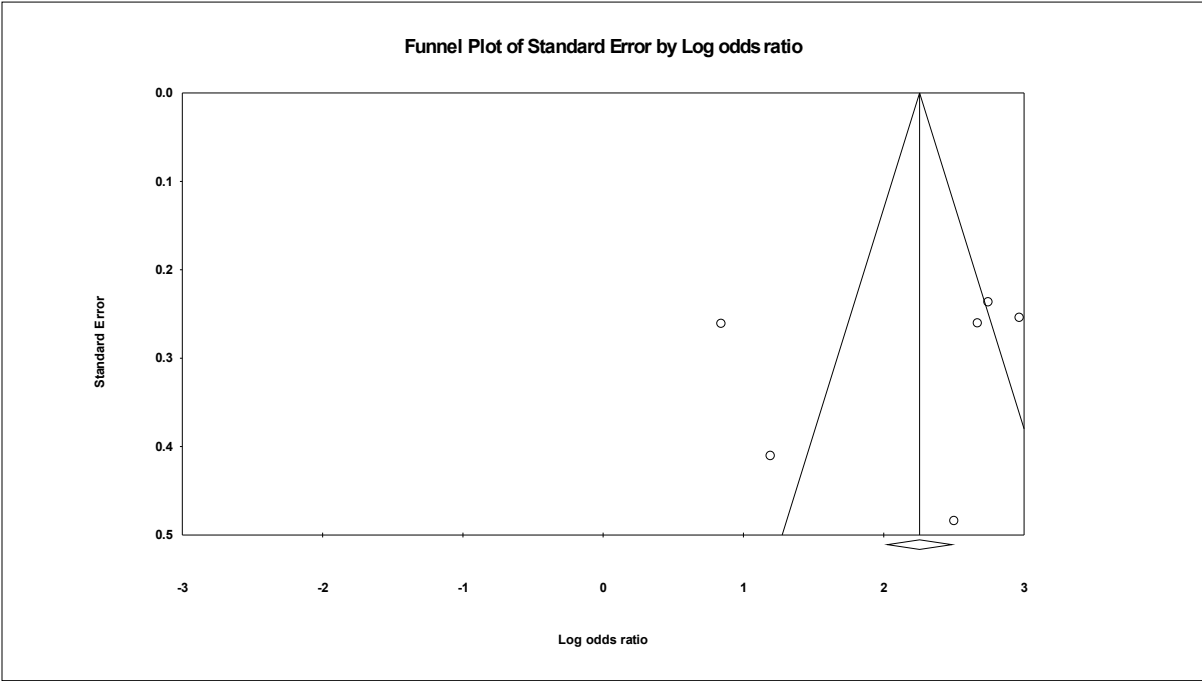
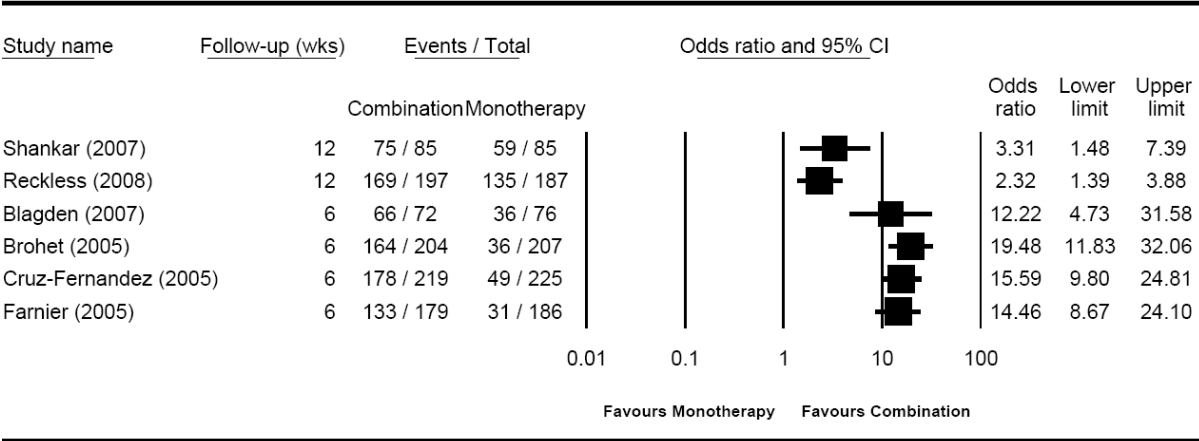
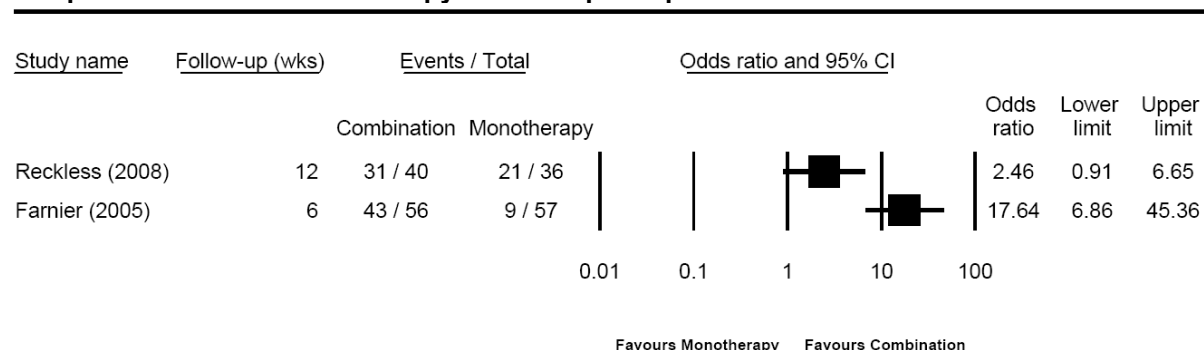
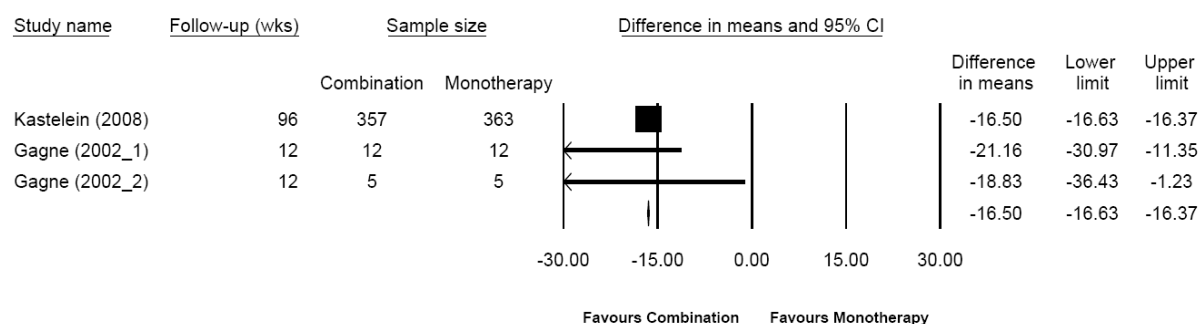


Figure G-34. Forest plots of achievement of ATP III LDL-c targets for ezetimibe plus statin therapy compared with statin monotherapy in female participants



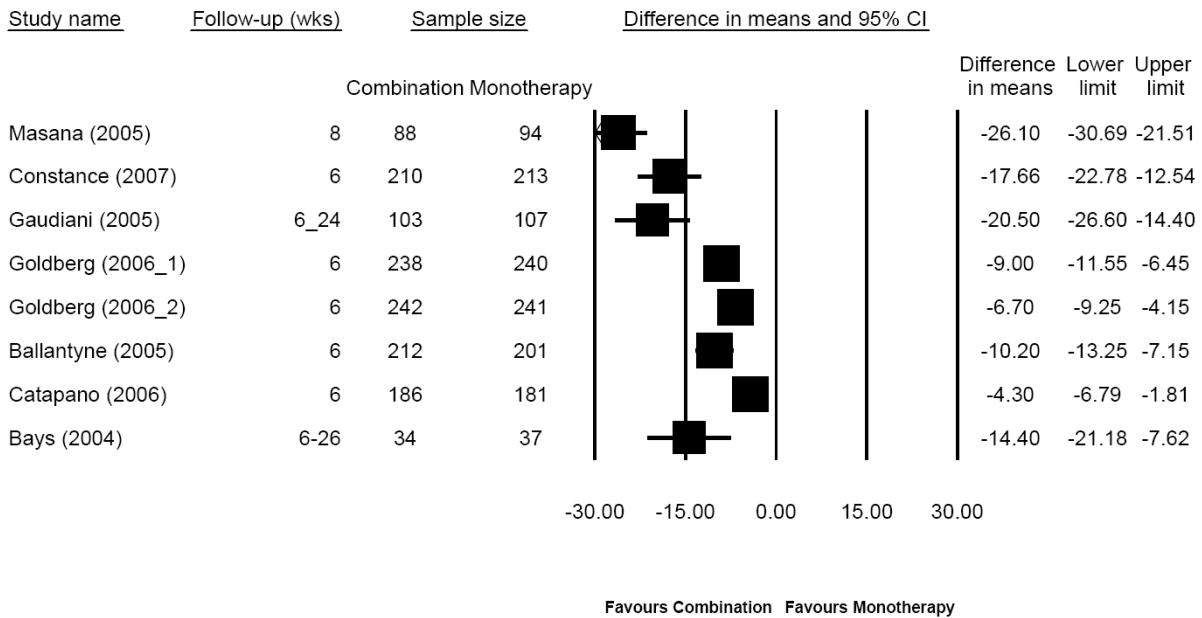
$I^2 = 87.38$

Figure G-35. Forest plot of LDL-c difference in mean percentage change from baseline, for ezetimibe plus statin therapy compared with statin monotherapy in participants with baseline LDL-c above 190 mg/dL



$I^2 = 0$

Figure G-36. Forest and funnel plots of LDL-c difference in mean percentage change from baseline, for ezetimibe plus statin therapy compared with statin monotherapy in participants with diabetes mellitus



$I^2 = 92.70$

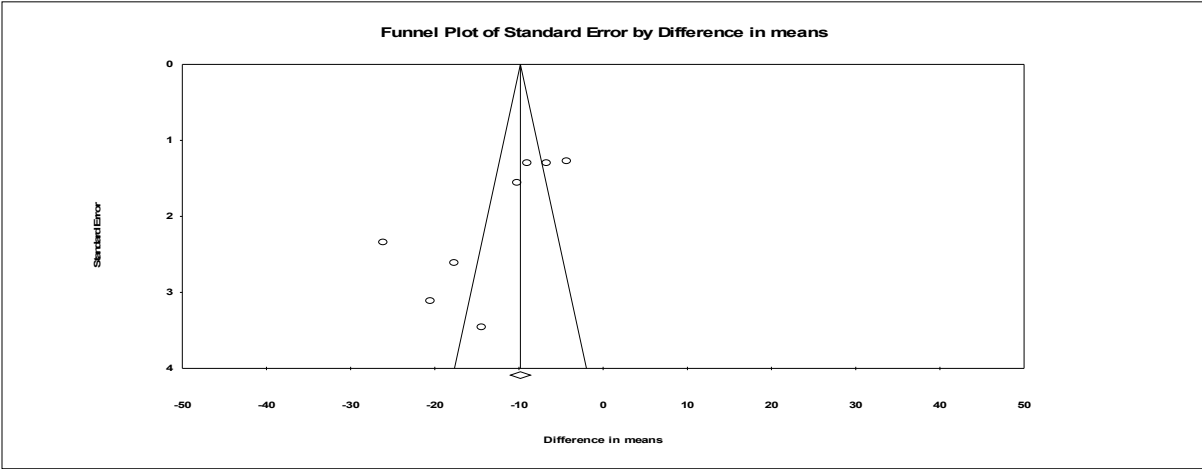


Figure G-37. Forest plot of LDL-c difference in mean percentage change from baseline, for ezetimibe plus statin therapy compared with statin monotherapy in participants with established vascular disease

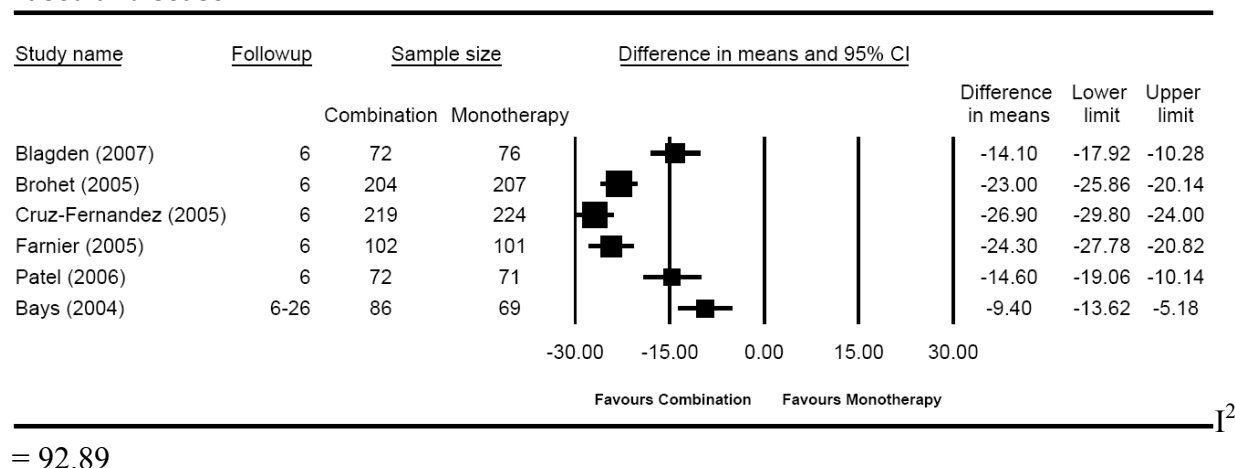


Figure G-38. Forest plot of LDL-c difference in mean percentage change from baseline, for ezetimibe plus statin therapy compared with statin monotherapy in participants of African descent

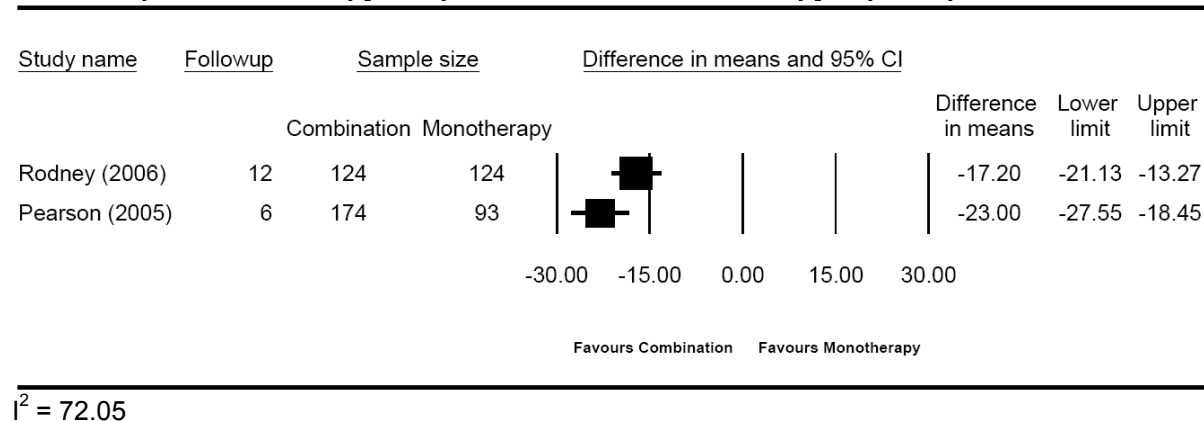
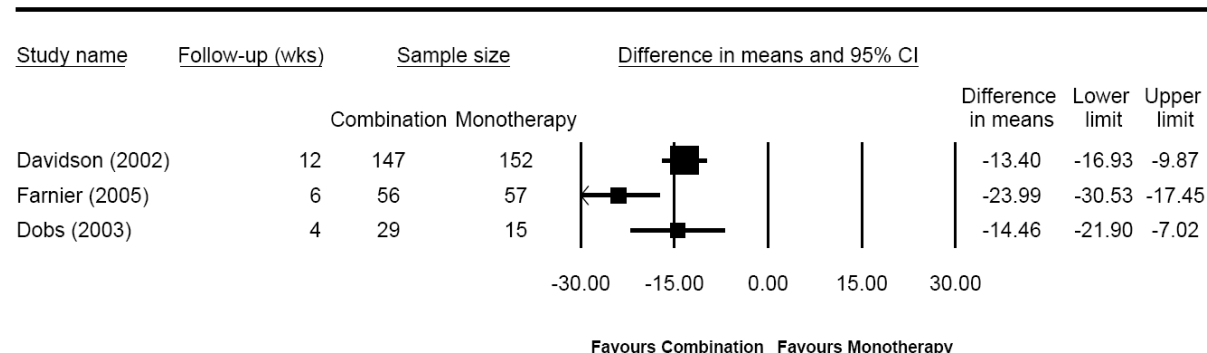
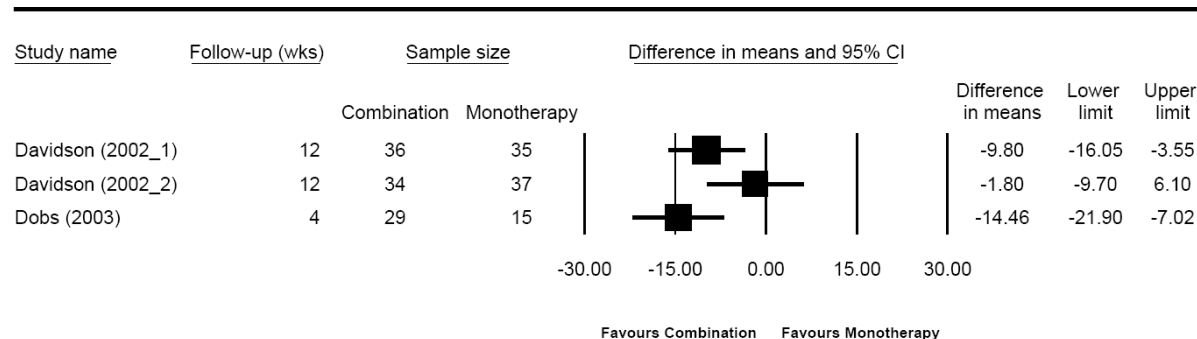


Figure G-39. Forest plot of LDL-c difference in mean percentage change from baseline, for ezetimibe plus statin therapy compared with statin monotherapy in female participants



$I^2 = 74.68$

Figure G-40. Forest plot of LDL-c difference in mean percentage change from baseline, for ezetimibe plus lower dose simvastatin therapy compared with higher dose simvastatin monotherapy in female participants



$I^2 = 62.45$

Figure G-41. Funnel plot of HDL-c difference in mean percentage change from baseline, for ezetimibe plus statin therapy compared with statin monotherapy in participants with diabetes mellitus

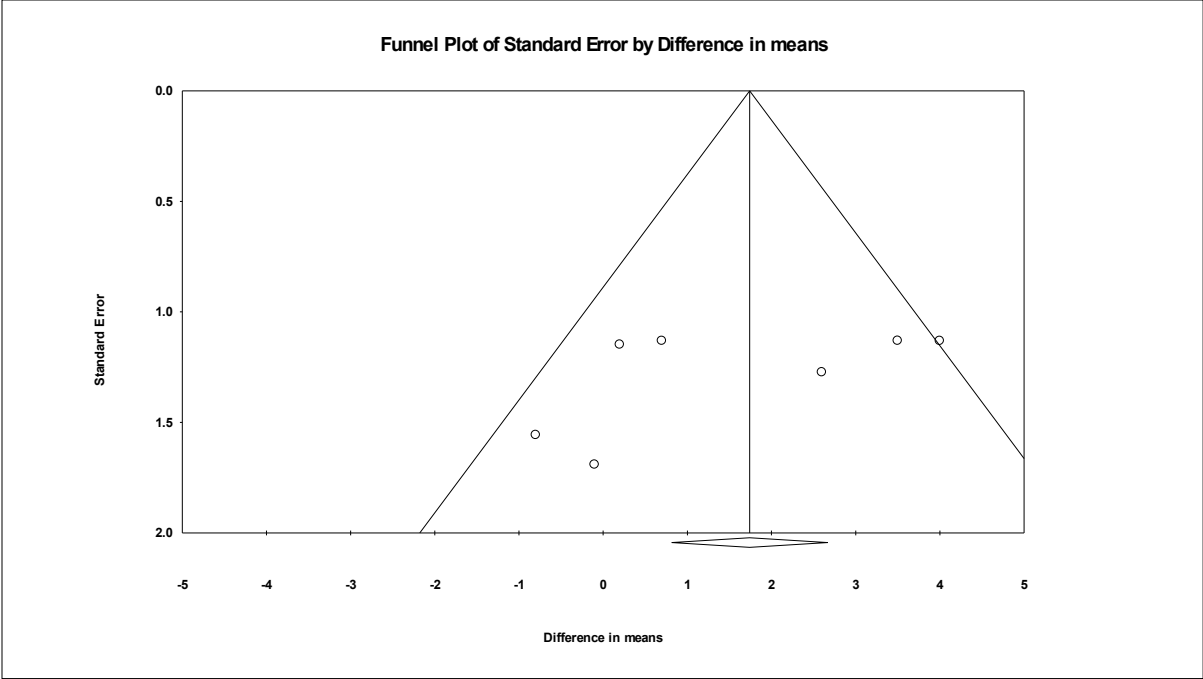


Figure G-42. Funnel plot of total cholesterol:HDL-c ratio difference in mean percentage change from baseline, for ezetimibe plus statin therapy compared with statin monotherapy in participants with diabetes mellitus

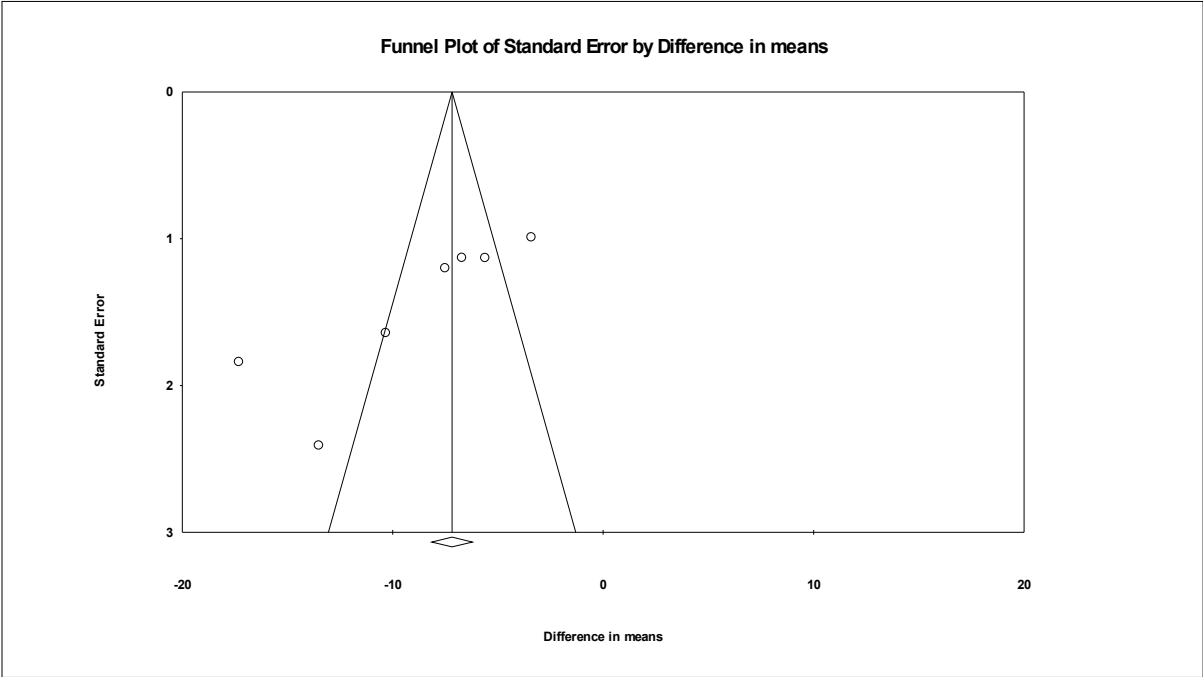
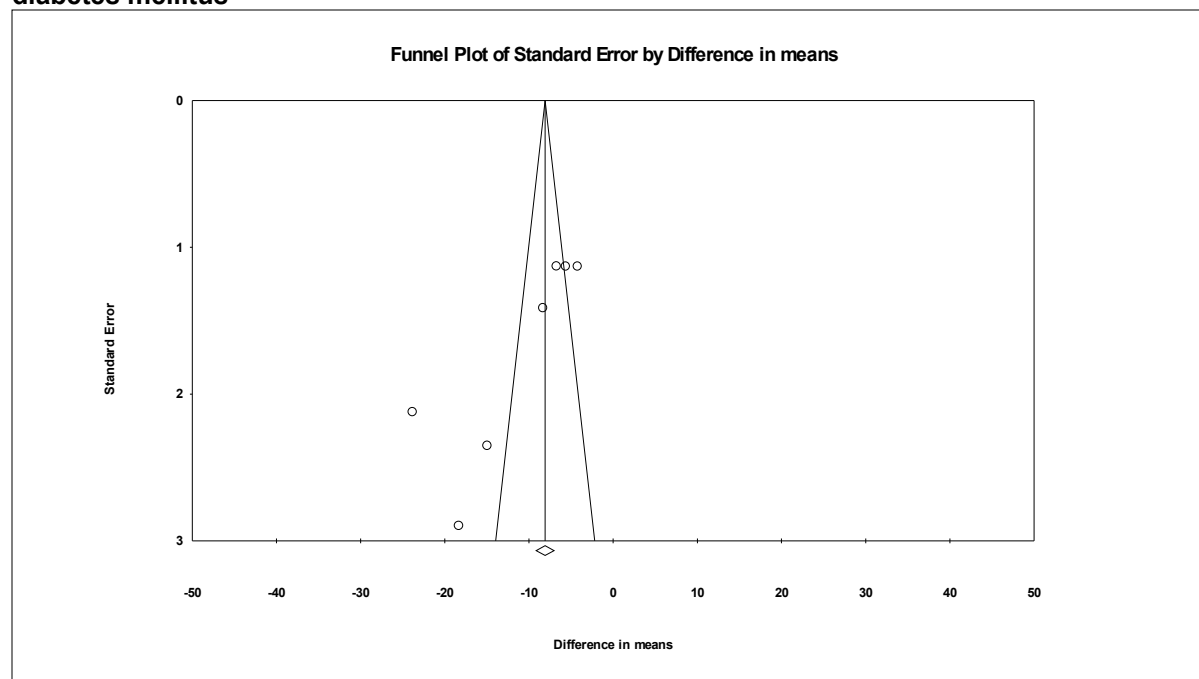
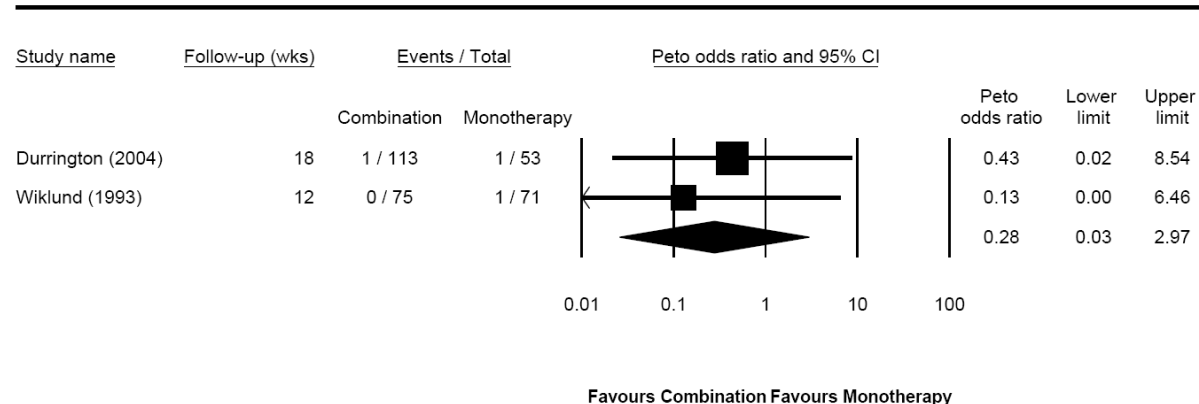


Figure G-43. Funnel plot of total non-HDL-c ratio difference in mean percentage change from baseline, for ezetimibe plus statin therapy compared with statin monotherapy in participants with diabetes mellitus



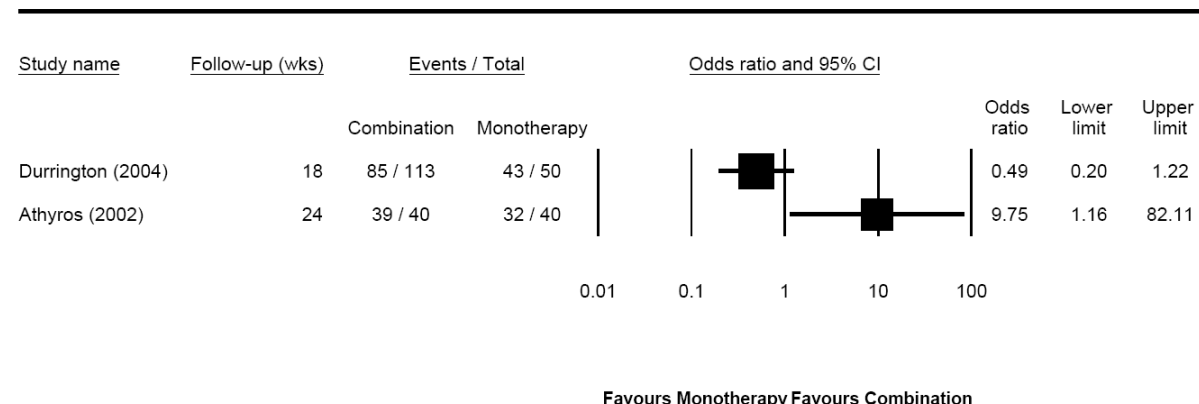
Forest and Funnel Plots: Fibrate - Statin Combination Therapy versus Statin Monotherapy

Figure G-44. Forest plot of all-cause mortality for fibrate-statin therapy compared with statin monotherapy, in all participants



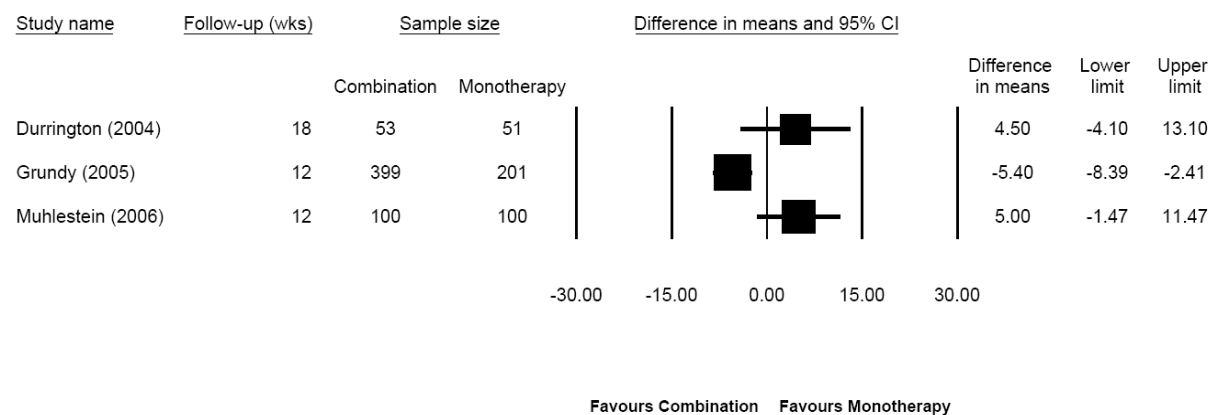
$I^2 = 0$

Figure G-45. Forest plot of achievement of ATP III LDL-c targets, for fibrate-statin therapy compared with statin monotherapy, in all participants, who required intensive lipid lowering therapy due to diabetes mellitus



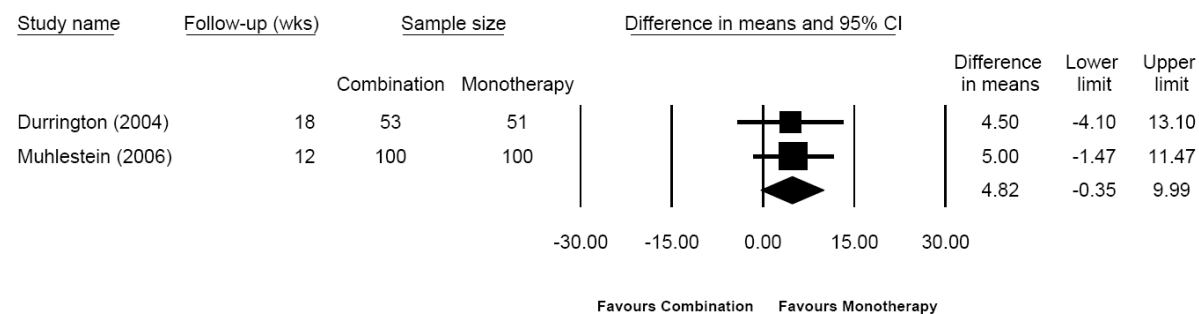
$I^2 = 84.31$

Figure G-46. Forest plot of difference in LDL-c mean percentage change from baseline for fibrate-statin therapy compared with statin monotherapy, in all participants



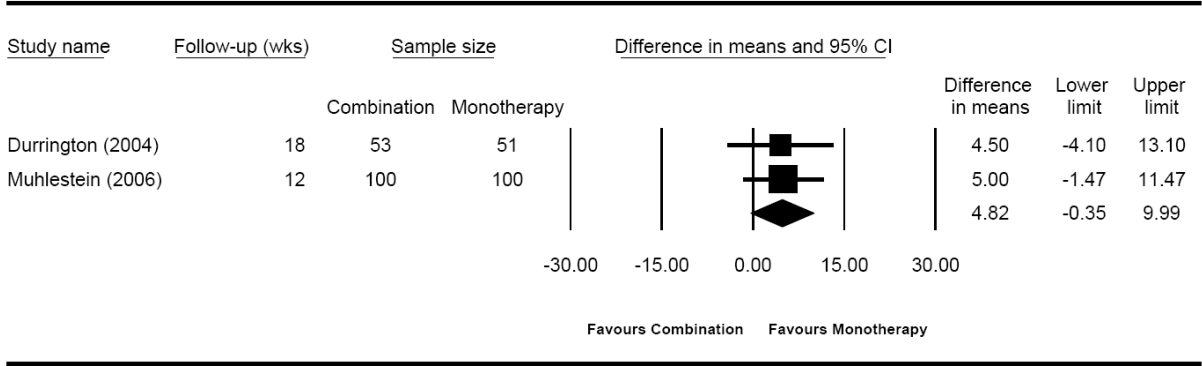
$I^2 = 82.22$

Figure G-47. Forest plot of difference in LDL-c mean percentage change from baseline for fibrate-statin therapy compared with statin monotherapy, in participants requiring intensive lipid lowering therapy



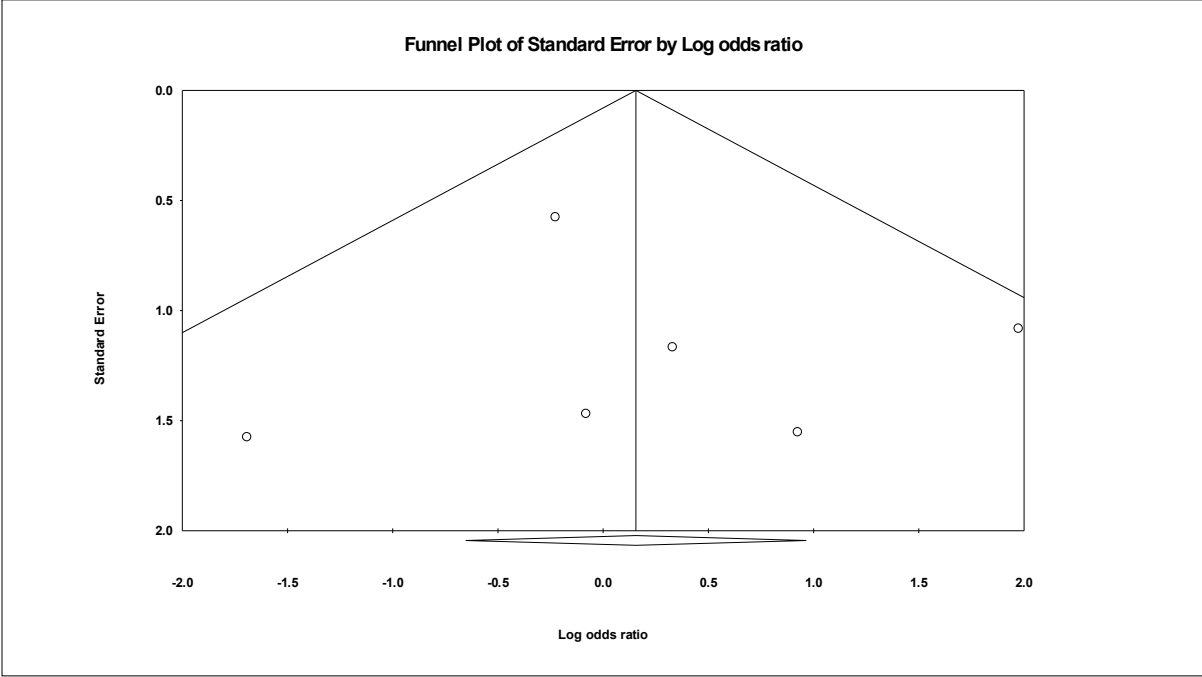
$I^2 = 0$

Figure G-48. Forest plot of difference in LDL-c mean percentage change from baseline for fibrate-statin therapy compared with statin monotherapy, in participants with diabetes mellitus



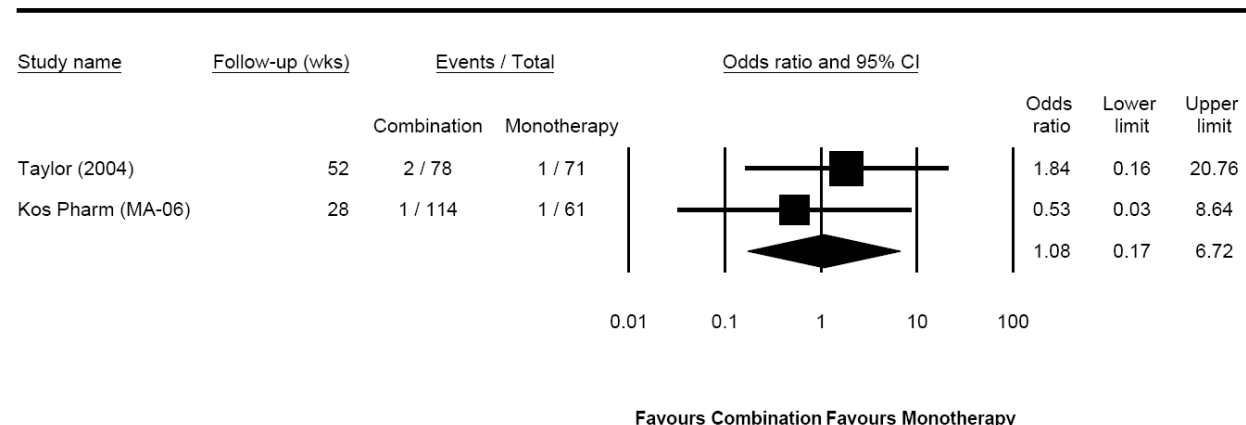
$I^2 = 0$

Figure G-49. Funnel plot of incidence of participants with myalgia, for fibrate-statin therapy compared with statin monotherapy, in all participants



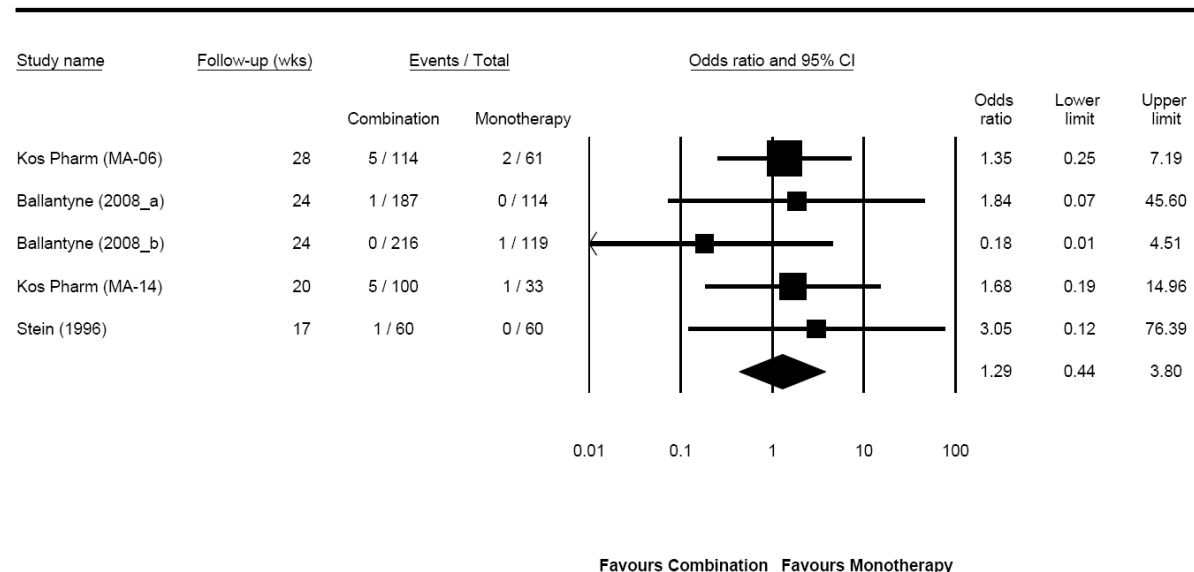
Forest and Funnel Plots: Niacin - Statin Combination Therapy Versus Statin Monotherapy

Figure G-50. Forest plot of all-cause mortality for niacin plus statin therapy compared with statin monotherapy, in all participants, in all trials with followup of 24 weeks or longer, and in all trials with adequate allocation concealment



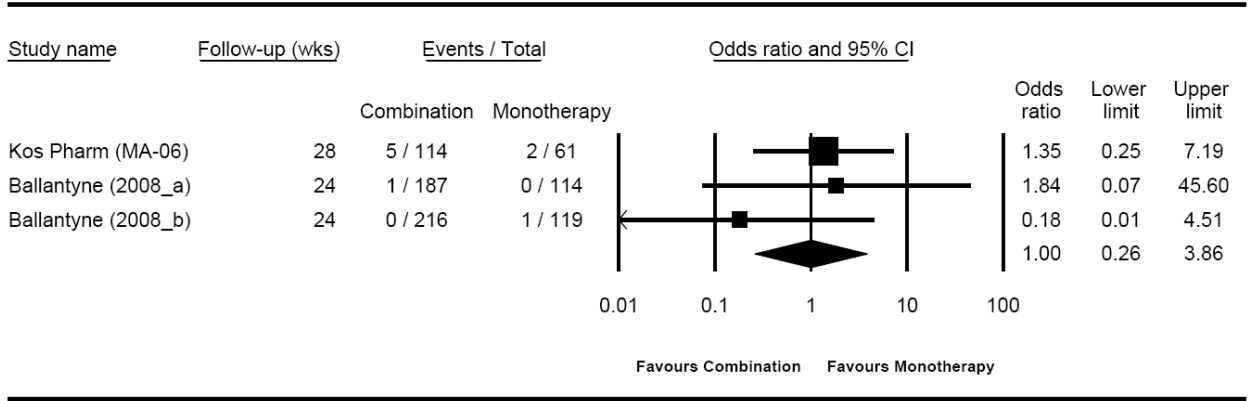
$I^2 = 0$

Figure G-51. Forest plot of serious adverse events for niacin plus statin therapy compared with statin monotherapy, in all participants



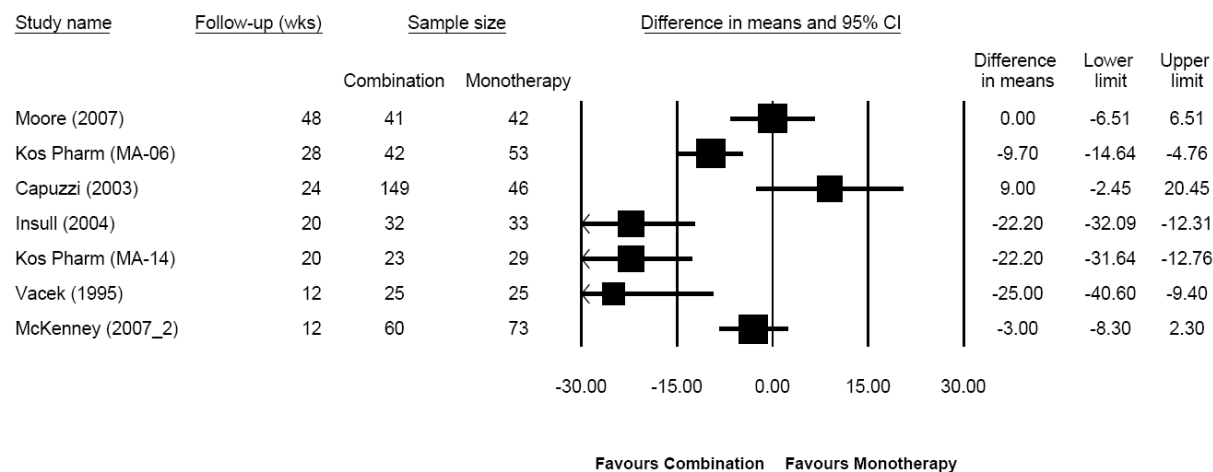
$I^2 = 0$

Figure G-52. Forest plot of serious adverse events for niacin plus statin therapy compared with statin monotherapy, in all participants, and in all trials with a followup of 24 weeks or longer



$I^2 = 0$

Figure G-53. Forest and funnel plots of difference in LDL-c mean percentage change from baseline for niacin plus statin therapy compared with statin monotherapy, in all participants



$I^2 = 85$

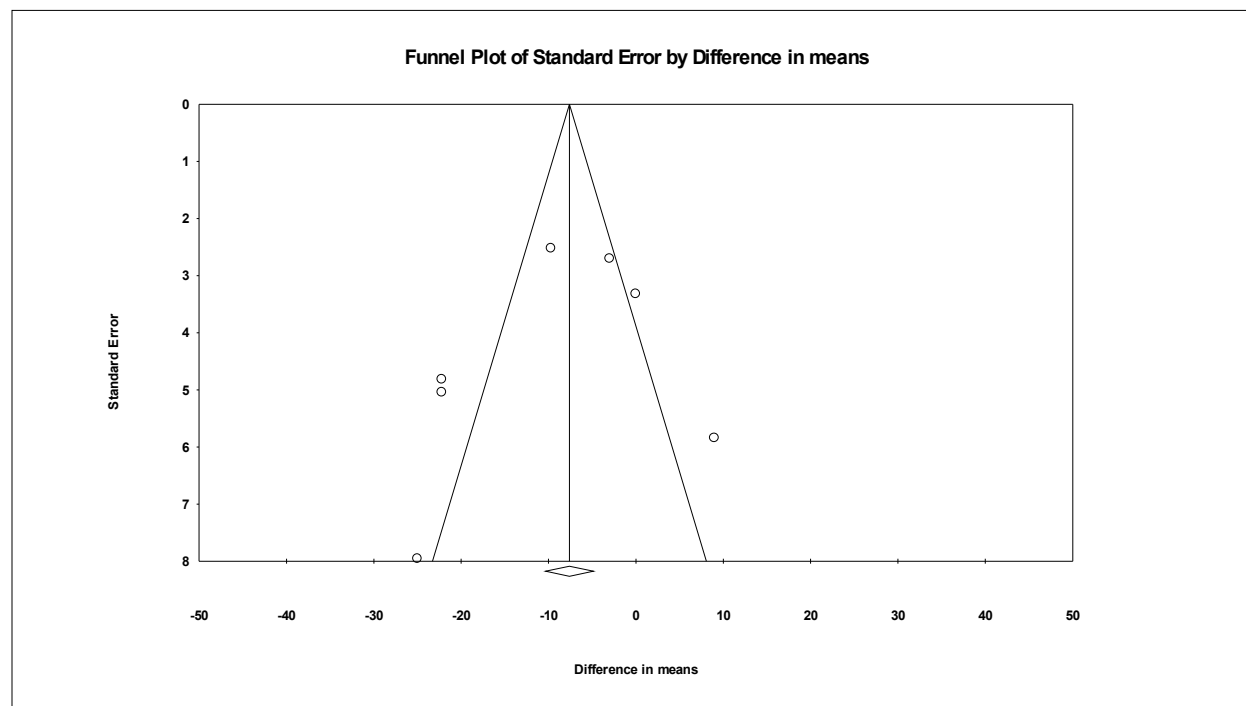


Figure G-54. Funnel plots of difference in HDL-c mean percentage change from baseline for niacin plus statin therapy compared with statin monotherapy, in all participants

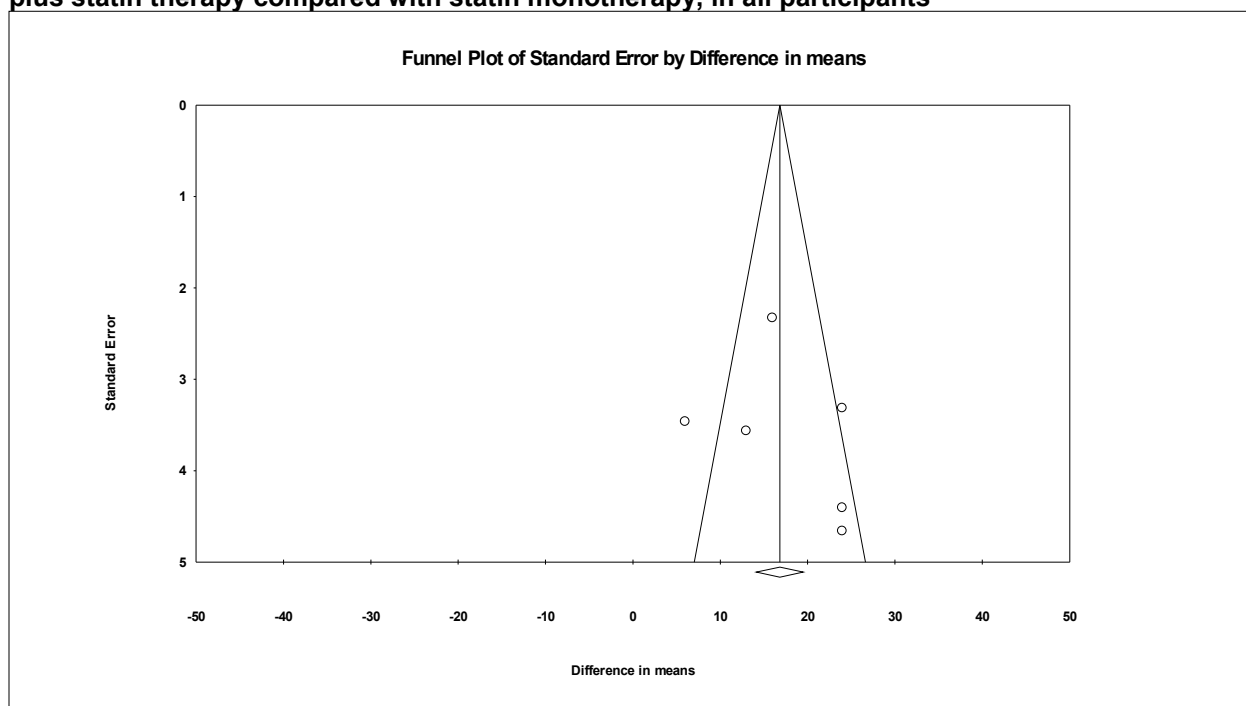


Figure G-55. Funnel plot of incidence of participants experiencing an adverse event, for niacin plus statin therapy compared with statin monotherapy, in all participants

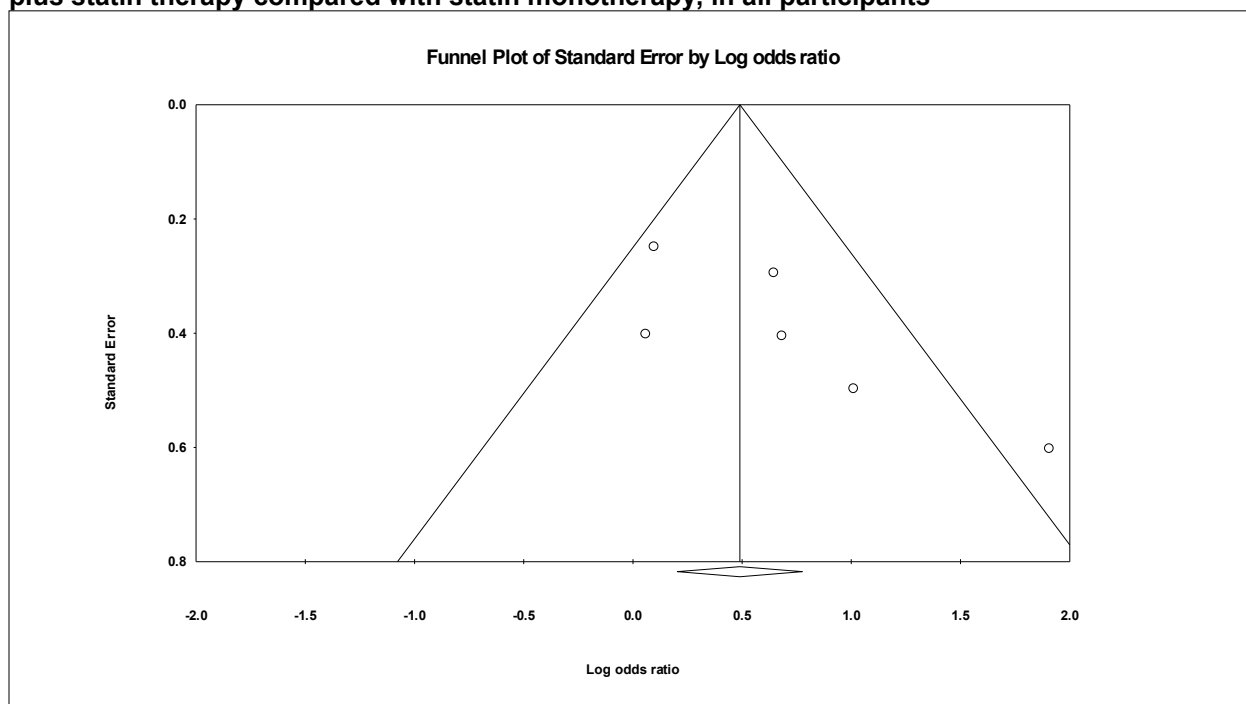
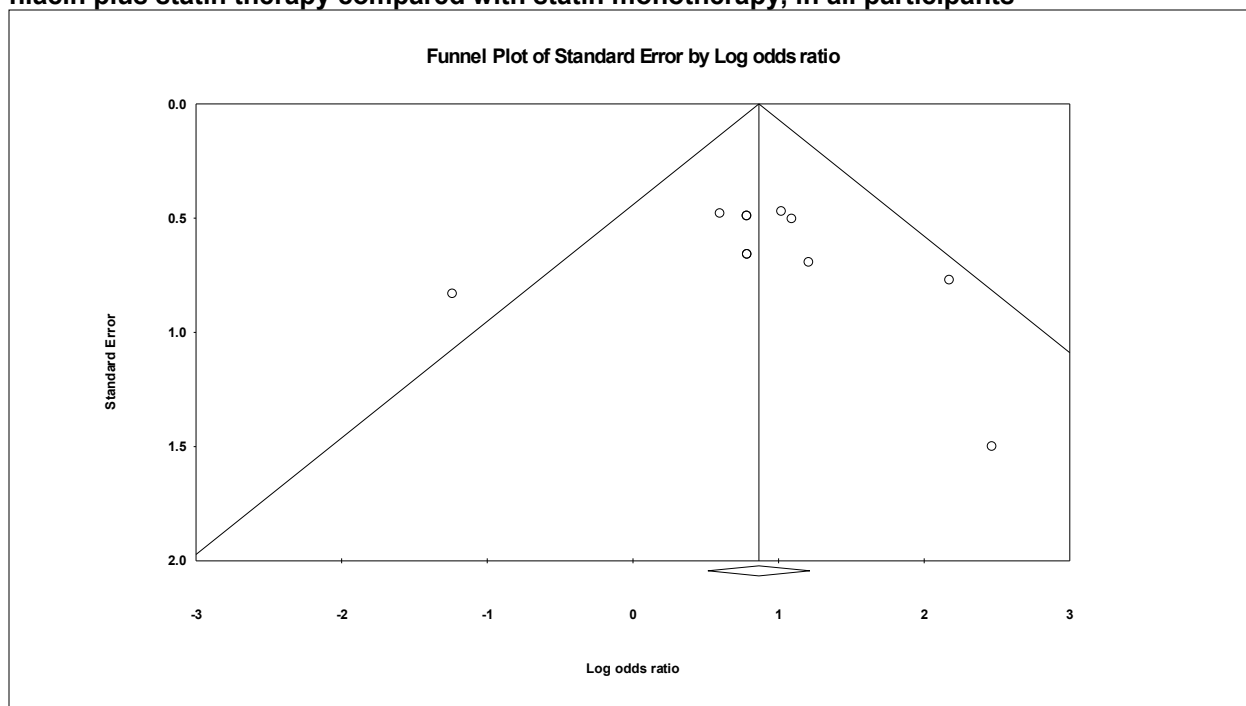
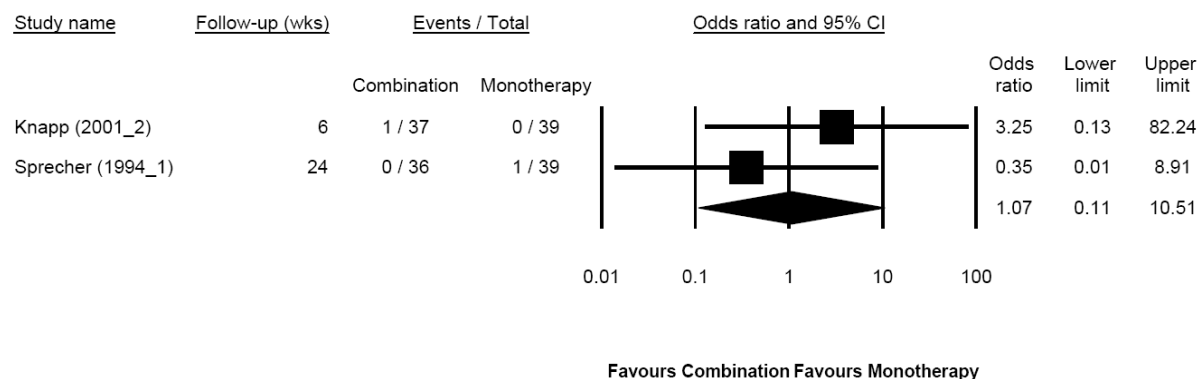


Figure G-56. Funnel plot of incidence of withdrawal from treatment due to an adverse event, for niacin plus statin therapy compared with statin monotherapy, in all participants



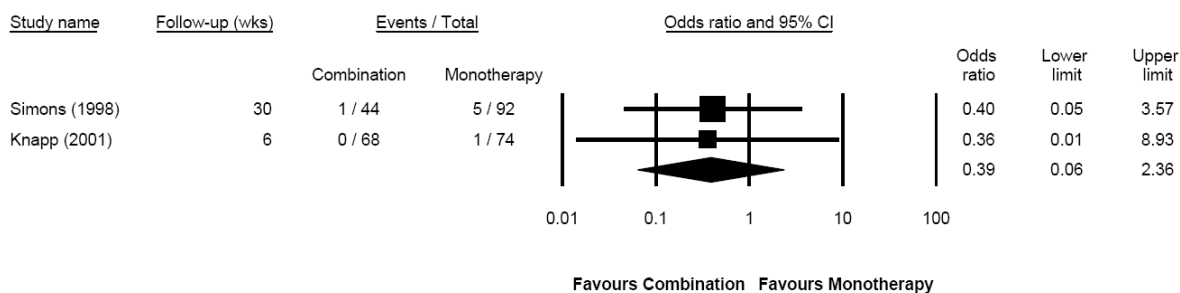
Forest and Funnel Plots: Bile Acid Sequestrant (BAS) - Statin Combination Therapy versus Statin Monotherapy

Figure G-57. Forest plot of all-cause mortality for BAS plus statin therapy compared with statin monotherapy, in all participants



$I^2 = 0$

Figure G-58. Forest plot of serious adverse events for BAS plus statin therapy compared with statin monotherapy, in all participants



$I^2 = 0$

Figure G-59. Forest and funnel plots with Egger’s regression test, of difference in LDL-c mean percentage change from baseline, for BAS plus statin therapy compared with statin monotherapy in all participants

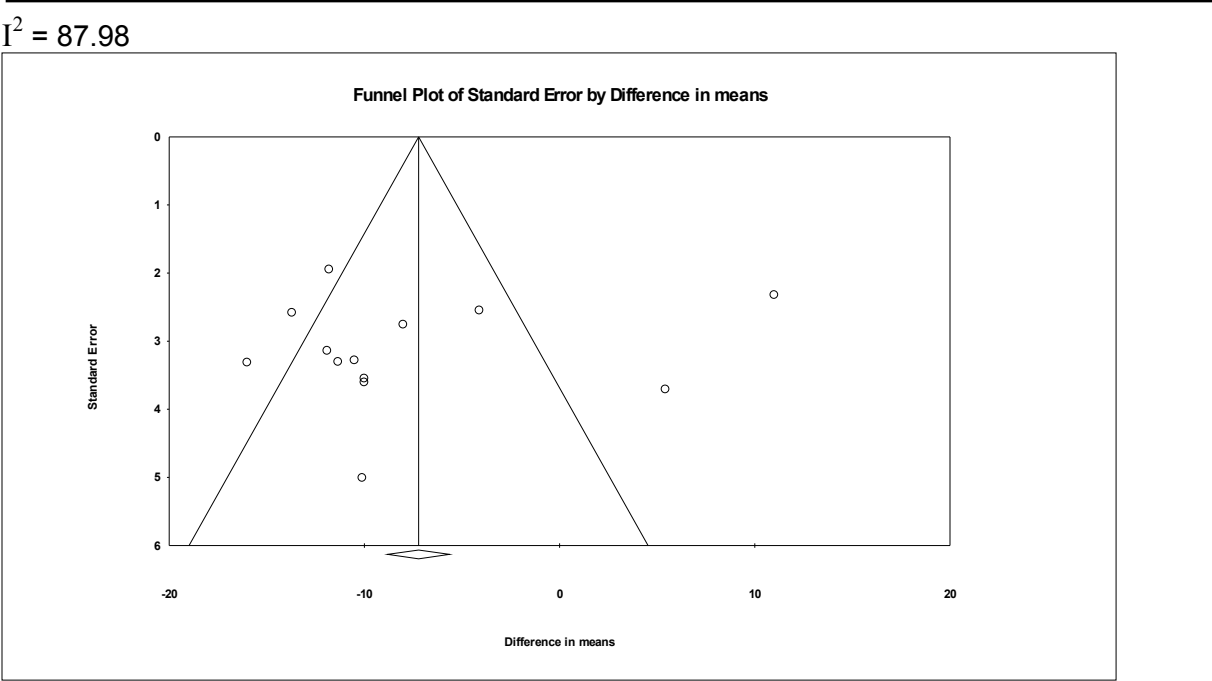
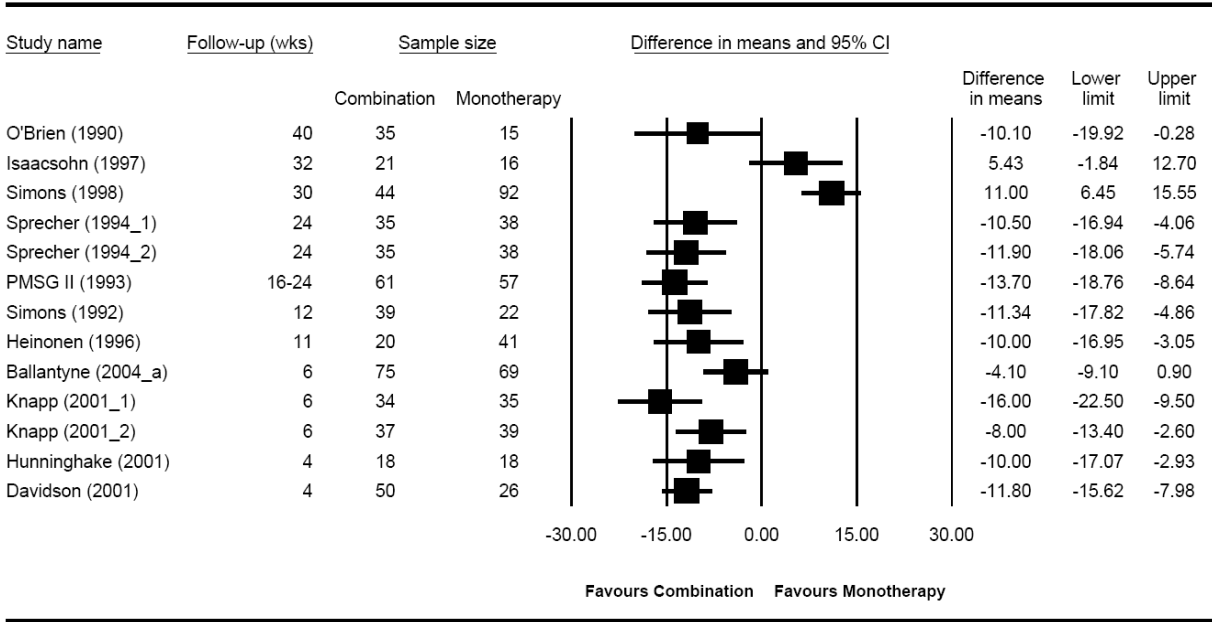
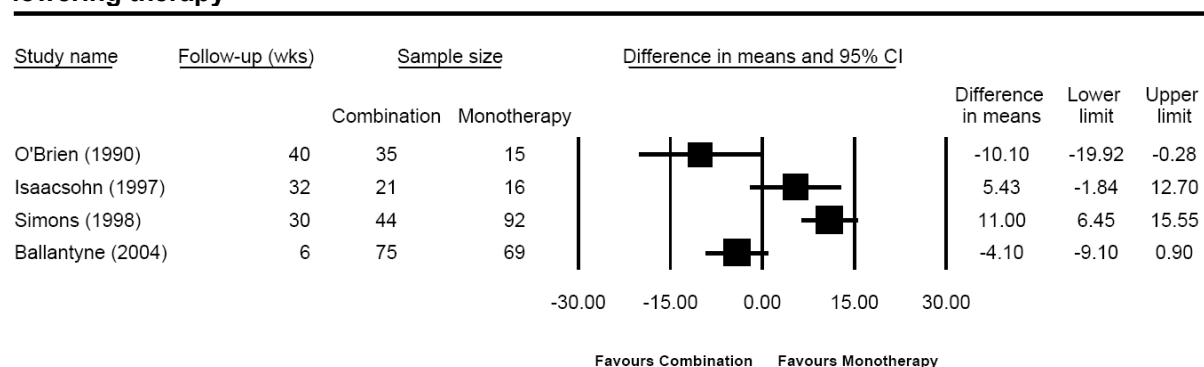
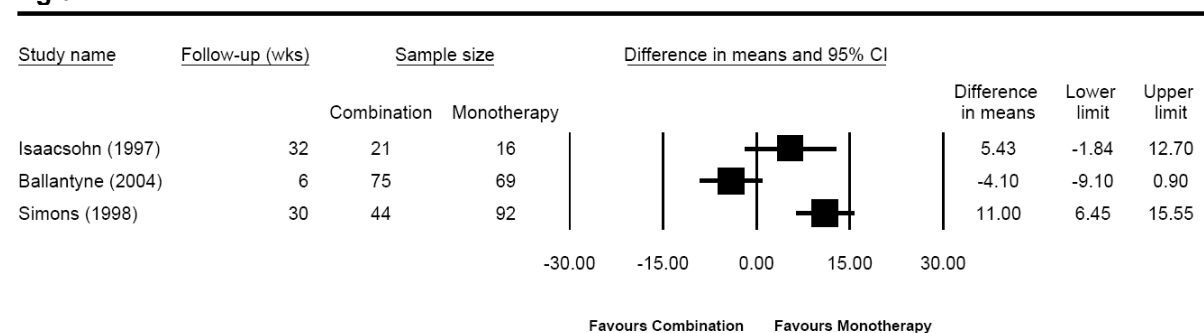


Figure G-60. Forest plot of difference in LDL-c mean percentage change from baseline for BAS plus statin therapy compared with statin monotherapy, in participants requiring intensive lipid lowering therapy



$I^2 = 88.84$

Figure G-61. Forest plot of difference in LDL-c mean percentage change from baseline, for BAS plus statin therapy compared with statin monotherapy, in participants with LDL-c above 190 mg/dL



$I^2 = 89.61$

Figure G-62. Funnel plot of treatment adherence on participants BAS plus statin therapy compared with statin monotherapy, in all participants

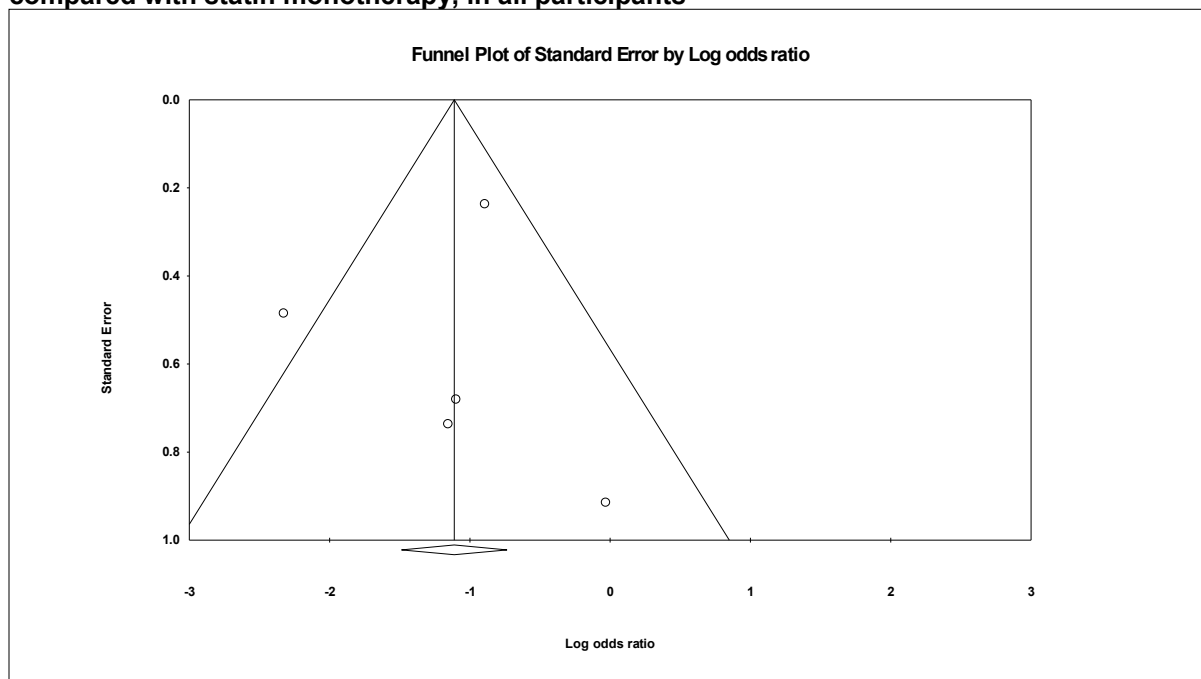


Figure G-63. Funnel plot of participants with adverse events for BAS plus statin therapy compared with statin monotherapy, in all participants

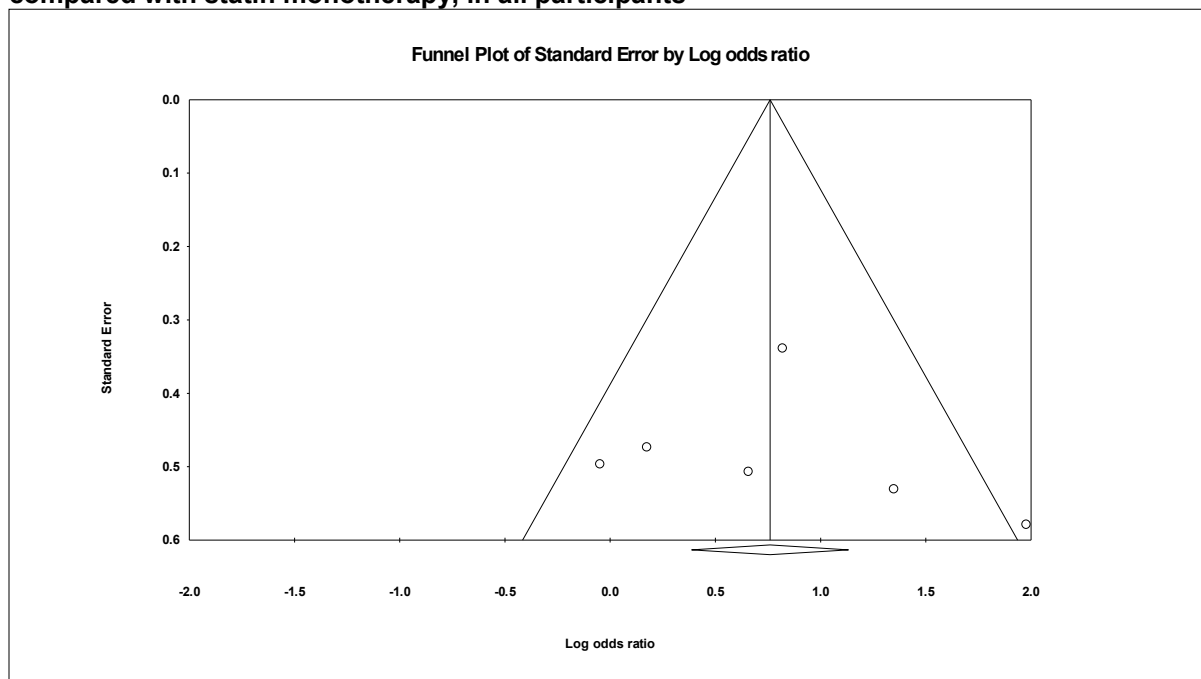
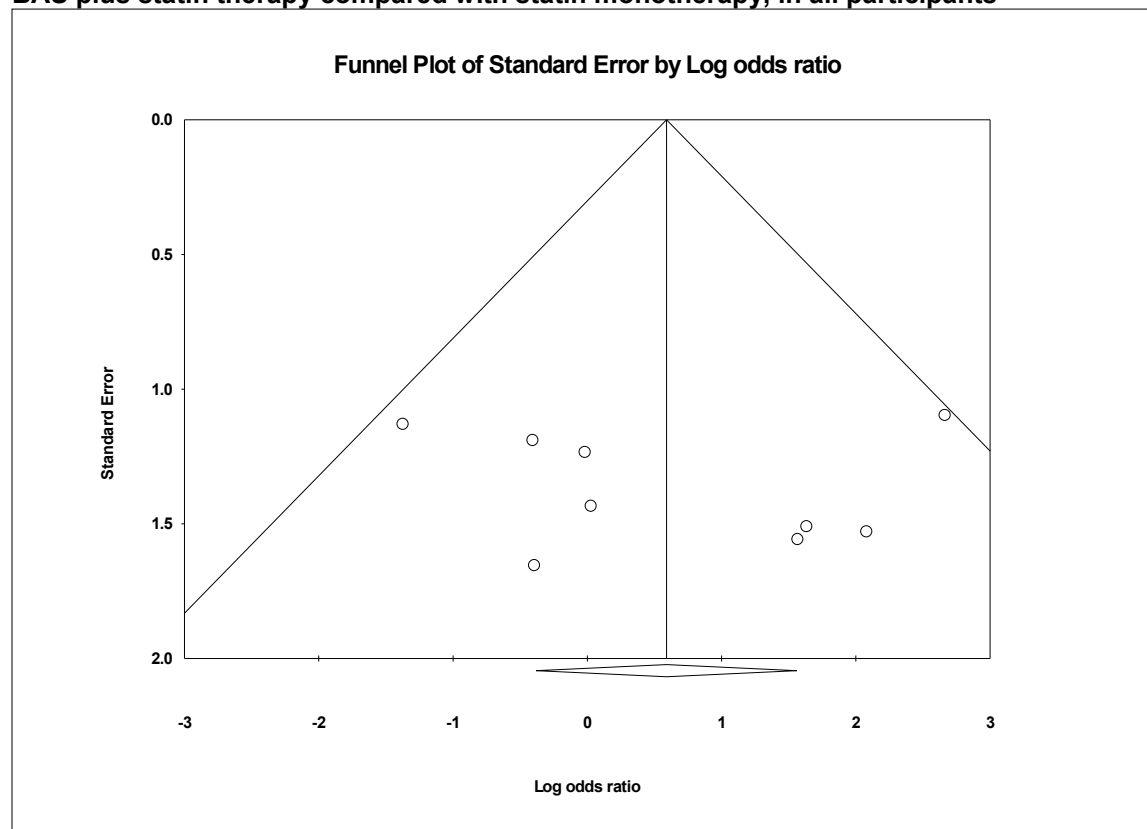
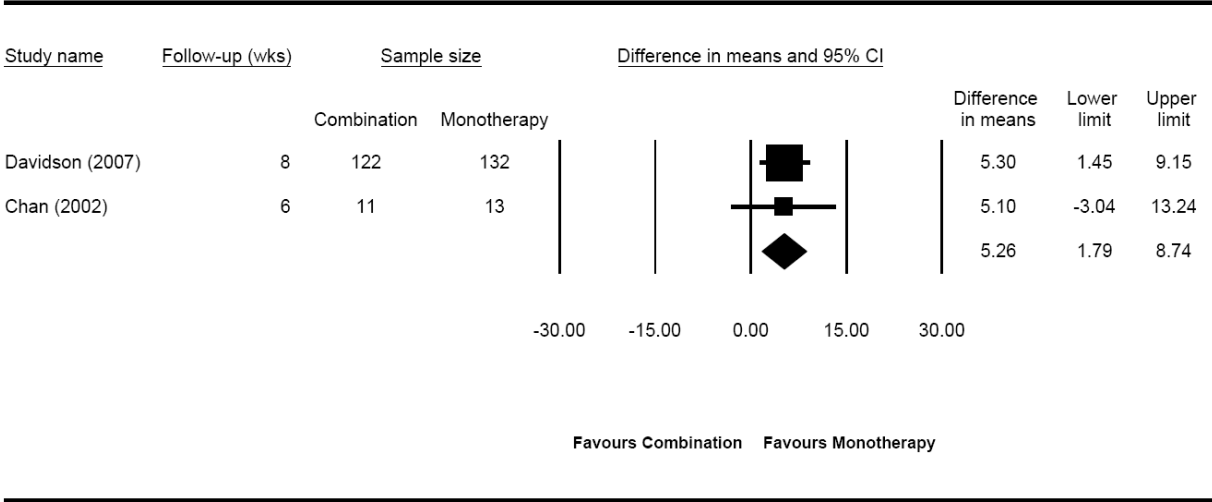


Figure G-64. Funnel plot of participants withdrawing from treatment due to adverse events for BAS plus statin therapy compared with statin monotherapy, in all participants



Forest Plot: Omega-3 Fatty Acid - Statin Combination Therapy versus Statin Monotherapy

Figure G-65. Forest plot of difference in LDL-c mean percentage change from baseline for omega-3 fatty acid plus statin therapy compared with statin monotherapy, in all participants



I² = 0

Appendix H: GRADE Tables, Assessing the Evidence

The following is compiled from GRADEProfiler software (version 3.2) and reproduced with permission, for convenience of the reader. A handbook with all recommendations can be found in: Schünemann H, Brozek J, Oxman A, editors. *GRADE handbook for grading quality of evidence and strength of recommendation. Version 3.2* [updated March 2008]. The GRADE Working Group, 2008. Available from <http://www.cc-ims.net/gradeupro>.

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.

GRADE Working Group: Rating the Quality of Evidence

Limitations to Evidence

Parameters	Rated as NO limitation	Rated as SERIOUS limitation	Rated as VERY SERIOUS limitation
Limitation in design	Negligible limitation	This may downgrade the quality of evidence by 1 level	This may downgrade the quality of evidence by 2 levels
Inconsistency			
Indirectness			
Imprecision			
Publication bias			

Explanation of Parameters

Parameter 1: Limitations to design of randomized controlled trials

Limitation	Explanation
Lack of allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in "pseudo" or "quasi" randomized trials with allocation by day of week, birth date, chart number etc.)
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Loss to follow-up and failure to adhere to the intention to treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other limitations	For example: <ul style="list-style-type: none">• stopping early for benefit observed in randomized trials, in particular in the absence of adequate stopping rules• use of unvalidated patient-reported outcomes• carry-over effects in cross-over trials• recruitment bias in cluster-randomized trials

Parameter 2: Inconsistency of results or unexplained heterogeneity

When heterogeneity exists, but investigators fail to identify a plausible explanation, the quality of evidence should be downgraded by one or two levels, depending on the magnitude of the inconsistency in the results.

Inconsistency may arise from differences in:

- populations (e.g. drugs may have larger relative effects in sicker populations)
- interventions (e.g. larger effects with higher drug doses)
- outcomes (e.g. diminishing treatment effect with time).

Parameter 3: Indirectness of evidence (*note: Indirect comparisons were not made in the present work*)

1. Indirect comparison – occurs when a comparisons of intervention A versus B is not available, but A was compared with C and B was compared with C. Such studies allow indirect comparisons of the magnitude of effect of A versus B. Such evidence is of lower quality than head-to-head comparisons of A and B would provide.
2. Indirect population, intervention, comparator, or outcome – the question being addressed by the guideline panel or by the authors of a systematic review is different from the available evidence regarding the population, intervention, comparator, or an outcome.

Parameter 4: Imprecision of results [dichotomous outcomes]

GRADE Working Group suggest downgrading the quality of evidence for any of the following three reasons:

1. total (cumulative) sample size is lower than the calculated “optimal information size” (OIS). OIS represents the number of patients generated by a conventional sample size calculation specifying a particular alpha and beta error, relative risk reduction, and baseline event rate.
2. total number of events is less than 300.
3. 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both negligible effect and appreciable benefit or appreciable harm. GRADE suggests that threshold for "appreciable benefit" or "appreciable harm" that should be considered for downgrading is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%.

Parameter 5: Publication bias

Publication bias arises when investigators fail to report studies they have undertaken (typically those that show no effect). Methods to detect the possibility of publication bias in systematic reviews exist, although authors of the reviews must often guess about the likelihood of publication bias. A prototypical situation that should elicit suspicion of publication bias occurs

when published evidence is limited to a small number of trials, all of which are showing benefits of the studied intervention.

The following abbreviations apply to all GRADE tables in Appendix H: 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 = confidence interval, LDL-c = low density lipoprotein cholesterol, HC = hypercholesterolemia, CAD = coronary artery diseases, CHD = coronary heart diseases, T2DM = type 2 diabetes mellitus

Operationalization of Parameters

Parameters	Rated as NO limitation	Rated as SERIOUS limitation	Rated as VERY SERIOUS limitation
Limitation in design	<ul style="list-style-type: none"> Adequate allocation concealment Adequate blinding procedure Intention-to-treat analysis 	Not all parameters were fulfilled, although some studies reported adequate allocation concealment or blinding or ITT	All parameters were unclear or inadequate
Inconsistency	<ul style="list-style-type: none"> No substantial heterogeneity (I-squared 50% or less) Populations in need of intensive treatment and subgroups Evidence-based on a single study 	<ul style="list-style-type: none"> Not all parameters were fulfilled. For example, although analysis could be pooled for a common drug effect, populations were clinically diverse Analysis of various doses and statins were considered inconsistent 	Diverse population and Substantial statistical heterogeneity
Indirectness	<ul style="list-style-type: none"> All studies were direct comparative trials Populations in need of intensive treatment and subgroups 	<ul style="list-style-type: none"> Analysis of various statin doses Analysis in populations other than in need of intensive treatment or subgroups 	Not used in the current review
Imprecision	95% confidence interval around the pooled data (or single estimate) was precise	<ul style="list-style-type: none"> Wide 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect and including both negligible effect and appreciable benefit or appreciable harm No events reported in a particular outcome If data not pooled and total number of events on evaluable participants were less than 300 	Very wide 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect and including both negligible effect and appreciable benefit or appreciable harm
Publication bias	Evidence based in more than 10 trials with nonsignificant Egger's test	Evidence is limited to 10 or fewer trials limiting interpretation of publication bias	Evidence based in more than 10 trials with significant Egger's test for asymmetry

Parameters not used	
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Limitation in design	Selective reporting outcome and/or other limitations – as it was not collected in our review
Inconsistency	Outcomes were given the same strength, as we decided in 3 clinical outcomes and 1 surrogate outcome judge to be as relevant as the clinical outcomes
Indirectness	Outcomes were given the same strength, as we decided in 3 clinical outcomes and 1 surrogate outcome judge to be as relevant as the clinical outcomes
Imprecision	Total sample size being lower than the calculated OIS

GRADE: Ezetimibe-Statin Combination Therapy Compared With Statin Monotherapy

Table H-1. GRADE: Ezetimibe-lower dose simvastatin combination therapy versus higher dose simvastatin monotherapy in participants requiring intensive lipid-lowering therapy

Quality assessment							Summary of findings					Quality	Importance
							No of patients		Effect				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Lower dose simvastatin-ezetimibe combination therapy	higher dose simvastatin monotherapy	Relative (95% CI)	Absolute			
All cause mortality (follow-up 12-24 weeks)													
2	randomised trial	very serious ¹	no serious inconsistency ²	no serious indirectness	very serious ¹	reporting bias ¹	0/214 (0%)	0/225 (0%)	not pooled	not pooled	VERY LOW	CRITICAL	
Vascular death - not measured													
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		CRITICAL	
Participants reaching ATP III LDL-c goals (follow-up 12-24 weeks)													
3	randomised trial ³	very serious ⁴	serious ⁵	no serious indirectness	very serious ⁵	reporting bias ⁴	198/256 (77.3%)	188/396 (47.5%)	not pooled	not pooled	VERY LOW	IMPORTANT	

1 Two trials reporting no deaths during a 12-24 weeks followup.^{121,151} One of the trials reported an appropriate method of randomization,¹⁵¹ no trial described method of allocation concealment, double-blind procedure and intention-to-treat analysis.

2 Participants with T2DM on stable medication, some of whom had previously completed a simvastatin trial, with LDL-c > 100 mg/dl

3 Fixed and/or conditional titration

4 Three trials included.^{47,121,151} One 12-week trial described appropriate method of randomization, and performed an intention-to-treat analysis for ATP III target outcome.¹⁵¹ None of the trials described double-blind procedure. Participants required intensive lipid-lowering therapy because of T2DM^{121,151} and/or CHD risk equivalent.^{47,151}

5 Data could not be pooled because of significant heterogeneity (I-squared = 60%)

Table H-2. GRADE: Ezetimibe-statin combination therapy versus statin monotherapy in participants requiring intensive lipid-lowering therapy

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe-statin combination therapy	statin monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 6-24)												
14 ¹	randomised trial	serious ^{1,2}	serious ²	serious ²	serious ³	none	6/3122 (0.2%)	9/3153 (0.3%)	OR 0.61 (0.22 to 1.71)	1 fewer per 1000 (from 2 fewer to 2 more)	VERY LOW	CRITICAL
Vascular death (follow-up mean 96 weeks)												
1	randomised trial	serious ⁴	no serious inconsistency	serious ⁴	serious ⁴	reporting bias ⁴	2/357 (0.6%)	1/363 (0.3%)	OR 1.98 (0.21 to 19.14) ⁵	3 more per 1000 (from 2 fewer to 51 more)	VERY LOW	CRITICAL
Participants reaching ATP III LDL-c goals (follow-up 6-24 weeks)												
18	randomised trial	serious ⁶	very serious ^{6,7}	serious ⁶	serious ⁷	none	3509/4265 (82.3%)	1833/3466 (52.9%)	not pooled	not pooled	VERY LOW	IMPORTANT

1 Seven trials reported no deaths.^{114,116,121,140,151,159,193}

2 One long-term¹²¹ and 13 short-term trials comparing different statins and different doses were included; funnel plot did not show significant asymmetry.^{114-116,118,140,142-144,149,151,159,193,194}

3 Six trials reported adequate allocation concealment,^{118,144,149,159,193,194} four reported an appropriate double-blind procedure,^{114-116,159} and one reported intention-to-treat analyses.¹⁴⁰

4 Wide confidence intervals in each single trial and pooled data

5 Single 96 weeks study comparing same dose statin in both arms.⁴² Study reported adequate allocation concealment and three vascular deaths.⁴² Double-blind, and intention-to-treat analysis procedures were not reported.⁴²

6 Peto OR

7 Eighteen short-term trials comparing different statins and different doses were included; funnel plot did not show significant asymmetry.^{47,112,114-118,121,140,142,144,148,149,151,167,168,193,194}

Seven trials reported an adequate allocation concealment,^{117,118,144,148,149,193,194} four appropriate double-blind procedure,^{114-116,148} and four reported intention-to-treat analyses.^{140,148,151,168}

7 Results not pooled because of significant heterogeneity (I-squared 90%). Participants required intensive lipid-lowering therapy because of primary HC (8 studies), HC with CAD (3 studies), CHD risk equivalent (3 studies), and DM (4 studies)

Table H-3. GRADE: Ezetimibe-statin combination therapy versus statin monotherapy in participants with baseline LDL-c > 190 mg/dL

Quality assessment							Summary of findings					Quality	Importance
							No of patients		Effect				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe-statin combination therapy	statin monotherapy	Relative (95% CI)	Absolute			
All cause mortality - not measured													
0	-	-	-	-	-	none	-	-	-	-		CRITICAL	
Vascular death (follow-up mean 96 weeks)													
1	randomised trial	serious ¹	no serious inconsistency	serious ¹	serious ¹	reporting bias ¹	2/357 (0.6%)	1/363 (0.3%)	OR 1.98 (0.21 to 19.14) ²	3 more per 1000 (from 2 fewer to 51 more)	VERY LOW	CRITICAL	
Participants reaching ATP III LDL-c goals - not measured													
0	-	-	-	-	-	None	-	-	-	-		IMPORTANT	

¹ Single 96 weeks study comparing same dose statin in both arms. ⁴² Study reported adequate allocation concealment and three vascular deaths. ⁴² Double-blind, and intention-to-treat analysis procedures were not reported. ⁴²

² Peto OR

Table H-4. GRADE: Ezetimibe-statin combination therapy versus statin monotherapy in participants with diabetes mellitus

Quality assessment							Summary of findings					Quality	Importance
							No of patients		Effect				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe-statin combination therapy	statin monotherapy	Relative (95% CI)	Absolute			
All cause mortality (follow-up 6-24 weeks)													
6	randomised trial	serious ¹	serious ¹	serious ¹	serious ²	reporting bias ¹	2/1509 (0.1%)	4/1507 (0.3%)	OR 0.40 (0.08 to 2.09)	2 fewer per 1000 (from 3 fewer to 3 more)	VERY LOW	CRITICAL	
Vascular death - not measured													
0	-	-	-	-	-	None	-	-	-	-		CRITICAL	
Participants reaching ATP III LDL-c goals (follow-up 6-24 weeks)													
9	randomised trial	serious ³	very serious ^{3,4}	serious ³	serious ⁴	reporting bias ³	2055/2474 (83.1%)	1074/1866 (57.6%)	not pooled	not pooled	VERY LOW	IMPORTANT	

1 A 24-week trial with unclear allocation concealment, double-blind procedure and no intention-to-treat analysis reported no deaths.¹²¹ Data from five 6-12 week trials reporting 6 deaths were pooled.^{118,144,149,193,194} All 6-12 week trials reported adequate allocation concealment, none reported double-blind procedure or intention-to-treat analysis. Included trials compared different statins and different doses.

2 Wide confidence intervals in each single trial and pooled data

3 Nine 6-24 week trials comparing different statins and different doses were included.^{115,117,118,121,144,149,167,193,194} Six trials reported adequate allocation concealment,^{117,118,144,193,194,259} one reported appropriate double-blind procedure,¹¹⁵ and none performed intention-to-treat analysis.

4 Short-term trials with significant heterogeneity (I-squared = 91%)

Table H-5. GRADE: Ezetimibe-statin combination therapy versus statin monotherapy in participants with established vascular disease

Quality assessment							Summary of findings					Quality	Importance
							No of patients		Effect				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe-statin combination therapy	statin monotherapy	Relative (95% CI)	Absolute			
All cause mortality (follow-up 6-12 weeks)													
6	randomised trial	serious ¹	serious ¹	serious ¹	serious ²	reporting bias ¹	4/970 (0.4%)	6/993 (0.6%)	OR 0.66 (0.19 to 2.31)	2 fewer per 1000 (from 5 fewer to 8 more)	VERY LOW	CRITICAL	
Vascular death - not measured													
0	-	-	-	-	-	None	-	-	-	-		CRITICAL	
Participants reaching ATP III LDL-c goals (follow-up 6-12 weeks)													
6	randomised trial	serious ³	very serious ^{3,4}	serious ³	serious ⁴	reporting bias ⁴	785/956 (82.1%)	346/966 (35.8%)	not pooled	not pooled	VERY LOW	IMPORTANT	

1 Six short-term trials comparing different statins and different doses were included,^{114-116,140,143,149} three trials reported no deaths.^{114,116,140} One trial reported adequate allocation concealment,¹⁴⁹ three reported appropriate double-blind procedure,¹¹⁴⁻¹¹⁶ and one performed intention-to-treat analysis.¹⁴⁰

2 Wide confidence intervals in each single trial and pooled data.

3 Six short-term trials comparing different statins and different doses were included,^{114-116,140,149,168} three trials reported no deaths.^{114,116,140} One trial reported adequate allocation concealment,¹⁴⁹ three reported appropriate double-blind procedure,¹¹⁴⁻¹¹⁶ and two performed intention-to-treat analysis.^{140,168}

4 All studies favored combination therapy, however, due to significant heterogeneity (I-squared 72%) data was not pooled.

Table H-6. GRADE: Ezetimibe-statin combination therapy versus statin monotherapy in participants of African descent

Quality assessment							Summary of findings					Quality	Importance
							No of patients		Effect				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe-statin combination therapy	statin monotherapy	Relative (95% CI)	Absolute			
All cause mortality (follow-up mean 12 weeks)													
1	randomised trial ¹	serious ^{1,2}	no serious inconsistency	serious ²	very serious ¹	reporting bias ¹	0/124 (0%)	0/123 (0%)	-	-	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 ³	no serious inconsistency	serious ³	no serious imprecision	reporting bias ³	85/135 (63%)	24/73 (32.9%)	OR 3.47 (1.9 to 6.33)	437 more per 1000 (from 201 more to 683 more)	VERY LOW	IMPORTANT	

1 A single RCT with no deaths in combination or monotherapy was identified¹¹¹

2 A 12 week trial comparing the same dose of simvastatin in both arms, with an adequate allocation concealment and double-blind procedure, no intention-to-treat analysis¹¹¹

3 Data from a sub-group population of a single 6 weeks trial comparing mixed statins in combination and monotherapy.¹¹⁷ Main RCT with adequate allocation concealment; double blind procedure not described, no intention-to-treat analysis performed.¹¹⁷

Table H-7. GRADE: Ezetimibe-statin combination 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	Ezetimibe-statin combination therapy	statin 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	no serious inconsistency	serious ¹	serious	reporting bias ¹	46/71 (64.8%)	8/42 (19%)	OR 7.82 (3.14 to 19.45)	576 more per 1000 (from 271 more to 854 more)	VERY LOW	IMPORTANT

¹ Data from a sub-group population of a single 6 weeks trial comparing mixed statins in combination and monotherapy.¹¹⁷ Main RCT with adequate allocation concealment; double blind procedure not described, no intention-to-treat analysis performed.¹¹⁷

Table H-8. GRADE: Ezetimibe-statin combination versus statins monotherapy in female participants

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe-statin combination	statin monotherapy	Relative (95% CI)	Absolute		
All cause-mortality (follow-up 4-12 weeks)												
2	randomised trial	serious ¹	serious ¹	serious ¹	very serious ^{1,2}	reporting bias ¹	1/72 (1.4%)	1/56 (1.8%)	OR 0.95 (0.06 to 15.75)	1 fewer per 1000 (from 17 fewer to 208 more)	VERY LOW	CRITICAL
Vascular death - not measured												
0	-	-	-	-	-	None	-	-	-	-		CRITICAL
Participants reaching ATP III LDL-c goals (follow-up 6-12 weeks)												
2	randomised trial	very serious ³	very serious ^{3,4}	serious ³	very serious ⁴	reporting bias ³	74/96 (77.1%)	30/93 (32.3%)	not pooled	not pooled	VERY LOW	IMPORTANT

1 Data analyzed is a sub-group of the whole trial population. A 4-week trial described adequate allocation concealment, double blind procedure and performed intention-to-treat analysis.¹⁶⁹ A 12-week trial described an adequate allocation concealment, but did not report double-blind procedure or performed intention-to-treat analysis.¹⁴⁹ Trials compared different statins and different statin doses.

2 Wide confidence interval.

3 A sub-group of two trials provided data for this outcome.^{114,149} One trial described an appropriate allocation concealment,¹⁴⁹ one described an appropriate double-blind procedure,¹¹⁴ and none performed an intention-to-treat analysis. Trials compared different statins and different statin doses.

4 Data could not be pooled because of significant heterogeneity (I-squared = 87%)

Table H-9. GRADE: Ezetimibe-lower dose simvastatin combination therapy versus higher dose simvastatin monotherapy in all participants

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Lower dose simvastatin-ezetimibe combination therapy ¹¹	higher dose simvastatin monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 4-24 weeks)												
3	randomised trial	serious ^{1,2}	serious ²	serious ²	very serious ¹	reporting bias ¹	0/248 (0%)	0/291 (0%)	not pooled	not pooled	VERY LOW	CRITICAL
Vascular death (follow-up mean 12 weeks)												
1	randomised trial	serious ³	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	1/119 (0.8%)	0/123 (0%)	OR 8.05 (0.16 to 407.27) ⁵	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW	CRITICAL
Serious adverse events (follow-up 4-24 weeks)												
3	randomised trial	serious ⁶	serious ⁷	no serious indirectness	serious ⁴	reporting bias ⁶	31/530 (5.8%)	13/397 (3.3%)	OR 1.64 (0.85 to 3.19)	20 more per 1000 (from 5 fewer to 66 more)	VERY LOW	CRITICAL
Participants reaching ATP III LDL-c goals (follow-up 12-24 weeks)												
3	randomised trial	very serious ⁸	serious ^{9,10}	no serious indirectness	very serious ¹⁰	reporting bias ⁸	198/256 (77.3%)	188/396 (47.5%)	not pooled	not pooled	VERY LOW	IMPORTANT

1 Three 4-24 week trials were included and reported no deaths.^{121,151,169} Two trials described an appropriate method of randomization.^{151,169} One 4-week trial described adequate allocation concealment, double-blind procedure, and reported an intention-to-treat analysis.¹⁶⁹

2 Two trials reported that all participants diagnosed with T2DM on stable medication.^{121,151} In the third trial, participants of mixed 10 year CHD risk, with primary hyperlipidemia (LDL-c \geq 130 mg/dL) not controlled on simvastatin 20 mg/day.¹⁶⁹

3 One 12 week trial reported one vascular death.¹³⁰ This trial had an adequate allocation concealment and double-blind procedure, and did not perform an intention-to-treat analysis. However, only 2 of the 8 arms in this trial contributed data for this outcome¹³⁰

4 Wide confidence interval.

5 Peto OR

6 Three 4-24 week trials were included.^{47,121,169} One 4 week trial described adequate allocation concealment, double-blind procedure, and reported an intention-to-treat analysis.¹⁶⁹ All participants required intensive lipid-lowering therapy because of T2DM¹²¹ or CHD risk equivalent.^{47,151}

7 One trial reported that all participants diagnosed with T2DM on stable medication.¹²¹ In two trials, participants of mixed 10 year CHD risk.^{47,169}

8 Three trials included.^{47,121,151} One 12-week trial described adequate allocation concealment, and performed an intention-to-treat analysis.¹⁵¹ None of the trials described appropriate double-blind procedure. All participants required intensive lipid-lowering therapy because of T2DM^{121,151} or CHD risk equivalent.^{47,151}

9 Two trials reported that all participants diagnosed with T2DM on stable medication.^{121,151} In one trial, participants of mixed 10 year CHD risk.⁴⁷

10 Data could not be pooled because of significant heterogeneity (I-squared = 60%)

11 Fixed and/or conditional titration

Table H-10. GRADE - Ezetimibe-statin combination therapy versus statin monotherapy in all participants followed for more than 24 weeks

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe-statin combination therapy	statin monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 24-52 weeks)												
4	randomised trial	very serious ¹	Serious ^{1,2}	Serious ¹	very serious ²	reporting bias ¹	3/942 (0.3%)	0/486 (0%)	OR 7.51 (0.38 to 147.37)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW	CRITICAL
Vascular death (follow-up 96 weeks)												
1	randomised trial	no serious limitations ³	no serious inconsistency	no serious indirectness	very serious ³	reporting bias ³	2/357 (0.6%)	1/363 (0.3%)	OR 1.98 (0.21 to 19.14)	3 more per 1000 (from 2 fewer to 51 more)	VERY LOW	CRITICAL
Serious adverse events (follow-up 24-52 weeks)												
6	randomised trial	serious ⁴	serious ^{4,5,6}	serious ⁴	serious ⁶	reporting bias ⁴	137/1329 (10.3%)	54/564 (9.6%)	not pooled	not pooled	VERY LOW	CRITICAL
Participants reaching ATP III LDL-c goals - not measured												
0	-	-	-	-	-	None	-	-	-	-		IMPORTANT

1 Four 24-52 week trials comparing different statins and different statin doses were included.^{48,121,126,166} 3 reported no deaths.^{48,121,126} Two trials reported an adequate allocation concealment,^{48,166} one described an appropriate double-blind procedure,⁴⁸ and one trial performed an intention-to-treat analysis.¹⁶⁶

2 Results based on 3 deaths, and only one trial with analyzable data¹⁶⁶ In this trial, participants were diagnosed with renal disease and without definitive indication for cholesterol lowering

3 A 96 week trial reporting 3 vascular deaths comparing same dose statin in both arms was included.⁴² This trial reported an adequate allocation concealment and appropriate double-blind procedure, no intention-to-treat analysis was performed.⁴² All participants with familial hypercholesterolemia and LDL-c > 210 mg/dl.

4 Six trials comparing different statins and different statin doses were included.^{48,121,126,130,166,167} Three trials described adequate allocation concealment,^{48,130,166} and one trial described intention-to-treat analysis¹⁶⁶. An appropriate procedure for double-blinding was not described.

5 Participants of mixed risk in four trials,^{48,126,130,166} primary hypercholesterolemia,¹⁶⁷ or T2DM on stable medication.¹²¹

6 Results not pooled because of significant heterogeneity (I-squared = 56%)

Table H-11. GRADE - Ezetimibe-statin combination therapy versus statin monotherapy in all participants

Quality assessment							Summary of findings					Quality	Importance
							No of patients		Effect				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe-statin combination therapy	statin monotherapy	Relative (95% CI)	Absolute			
All cause mortality (follow-up 2-52 weeks)													
24	randomised trial	serious ¹	Serious ^{1,2}	serious ¹	serious ²	none	9/7867 (0.1%)	9/6540 (0.1%)	OR 0.95 (0.37 to 2.41) ³	0 fewer per 1000 (from 1 fewer to 1 more)	VERY LOW	CRITICAL	
Vascular death (follow-up 12-96 weeks)													
2	randomised trial	very serious ⁴	serious ⁵	serious ⁵	very serious ⁴	reporting bias ⁴	3/596 (0.5%)	1/600 (0.2%)	OR 2.70 (0.38 to 19.2) ³	3 more per 1000 (from 1 fewer to 35 more)	VERY LOW	CRITICAL	
Serious adverse events (follow-up 4-52)													
27	randomised trial	serious ⁶	serious ⁶	serious ⁶	no serious imprecision	none	297/7094(4.2%)	192/6369 (3%)	OR 1.08 (0.88 to 1.33)	3 more per 1000 (from 1 fewer to 35 more)	VERY LOW	CRITICAL	
Participants reaching ATP III LDL-c goals (follow-up 6-24 weeks)													
23	randomised trial	serious ⁷	Very serious ^{7,8,9}	serious ⁷	serious ⁹	none	6992/8646 (80.9%)	4337/7298 (59.4%)	not pooled	not pooled	VERY LOW	IMPORTANT	

1 Twenty four 2-52 week trials comparing different statins and different statin doses were included; funnel plot did not show significant asymmetry.^{48,110,111,114-118,121,126,127,129,140,142-144,149,151,158,159,166,169,193,194} 16 trials reported no deaths.^{48,110,111,114,116,117,121,126,127,129,140,151,158,159,169,193}

concealment,^{118,144,149,158,159,166,169,194} 4 trials described an adequate allocation concealment,^{115,158,159,169} and 5 trials performed an intention-to-treat analysis.^{110,151,166,169,187}

2 Results based on mixed population with scarce number of deaths (18 in total), and all but one trial¹⁶⁶ had a short-term follow up.

3 Peto OR

4 Two 12-96 week trials reported 4 vascular deaths.^{42,130} Both studies reported an adequate allocation concealment, but did not describe an appropriate double-blind procedure, nor performed an intention-to-treat analysis.

5 One short-term trial was performed in a mixed risk population,¹³⁰ and one long-term trial in participants with familial hypercholesterolemia and LDL-c > 210 mg/dl.⁴² All trials have used simvastatin with different doses.

6 Twenty seven 2-52 week trials comparing different statins and different statin doses were included; funnel plot did not show significant asymmetry.^{47,48,110-112,114-116,118,121,126,130,140,142-144,149,151,154,156,158,159,166-169,193}

Three trials did not report any SAEs.^{110,158,168} Twelve trials described an adequate allocation concealment,^{48,111,118,130,144,149,154,158,159,166,169,193} 9 trials described appropriate double-blind procedure,^{48,111,114-116,154,158,159,169} and 6 trials described intention-to-treat analysis.^{110,140,156,166,168,169}

7 23 short-term trials comparing different statins and different statin doses were included; funnel plot did not show significant asymmetry.^{47,112,114-118,121,126,127,129,130,140,142,144,148,149,151,156,167,168,193,194}

9 trials described adequate allocation concealment,^{117,118,127,130,144,148,149,193,194} 4 trials described appropriate double-blind procedure,^{114-116,148} and 7 trials described intention-to-treat analysis.^{127,129,140,148,151,156,168}

8 Participants with mixed risk: vascular disease,¹¹² CAD,^{114-116,140}, not ATP III target,^{117,118,167}, CHD risk equivalent,^{47,142} DM.^{121,144,151,156,194}, and primary hypercholesterolemia.^{126,127,129,130,148,149,168,193}

9 Results based only on short-term trials, with significant heterogeneity (I-squared = 93%)

GRADE: Fibrate-Statin Combination Therapy Compared With Statin Monotherapy

Table H-12. GRADE: Fenofibrate (67 mg/day)-Rosuvastatin (5-10 mg/day) combination therapy 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	Fenofibrate (67 mg/day)-rosuvastatin (5-10 mg/day) combination therapy	rosuvastatin (40 mg/day) monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 18 weeks)												
1	randomised trial	very serious ¹	no serious inconsistency	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)	11 fewer per 1000 (from 18 fewer to 109 more)	VERY LOW	CRITICAL
Vascular death - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Serious Adverse events - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Participants reaching ATPIII LDL-c goals (follow-up 18 weeks)												
1	randomised trial	very serious ¹	no serious inconsistency	no serious indirectness	very serious ^{1,2}	reporting bias ²	83/113 (73.5%)	43/50 (86%)	OR 0.49 (0.2 to 1.22)	358 fewer per 1000 (from 630 fewer to 121 more)	VERY LOW	IMPORTANT

1 Single study with unclear allocation concealment, no intention-to-treat analysis reported, short-term follow-up, and very sparse number of events.¹²⁵

2 Only one of the 11 included trials compared lower dose statin combination with higher dose monotherapy. All participants were diagnosed with T2DM.¹²⁵

Table H-13. Fibrate-statin combination therapy versus statin monotherapy in participants requiring intensive lipid-lowering therapy

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	all statins plus fibrates	statins monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 18 weeks)												
1	randomised trial	very serious ¹	no serious inconsistency	no serious indirectness	very serious ¹	reporting bias ¹	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 ²	no serious inconsistency	serious ²	very serious ²	reporting bias ²	0/25 (0%)	0/23 (0%)	-	-	VERY LOW	CRITICAL
Participants reaching ATPIII LDL-c goals (follow-up 18-24 weeks)												
2	randomised trial	very serious ³	serious ⁵	serious ³	very serious ⁵	reporting bias ⁶	124/153 (81%)	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 follow-up, and very sparse number of events.¹²⁵ All participants on the study had DM.

2 Single study comparing same dose of fluvastatin in both arms, with unclear allocation concealment, no intention-to-treat analysis reported. No SAEs were reported.¹²³

3 Two trials comparing different statins and different doses were included,^{125,161} none reported adequate allocation concealment or an appropriate double-blind procedure, one reported intention-to-treat analyses.¹⁶¹

4 All participants in both trials had diabetes mellitus.^{125,161}

5 Results based on two short-term trials, with significant heterogeneity (I-squared = 84%)

6 Results provided in only two out of 11 included trials.

Table H-14. GRADE: Fibrate-statin combination therapy versus statin monotherapy in participants with diabetes mellitus

Quality assessment							Summary of findings					Quality	Importance
							No of patients		Effect				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	statins plus fibrates	statins monotherapy	Relative (95% CI)	Absolute			
All cause mortality (follow-up 18 weeks)													
1	randomised trial	very serious ¹	no serious inconsistency	no serious indirectness	very serious ^{1,2}	reporting bias ¹	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 ³	Serious ⁴	serious ³	very serious ⁴	reporting bias ⁵	124/153 (81%)	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 follow-up, and very sparse number of events.¹²⁵

2 Wide confidence interval.

3 Two trials comparing different statins and different doses were included,^{125,161} none reported adequate allocation concealment or an appropriate double-blind procedure, one reported intention-to-treat analyses.¹⁶¹

4 Results based on two short-term trials, with significant heterogeneity (I-squared = 84%)

5 Results provided in only two out of 11 included trials

Table H-15. GRADE - Fibrate-statin combination therapy versus statin monotherapy in all participants followed for more than 24 weeks

Quality assessment							Summary of findings					Quality	Importance
							No of patients		Effect				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Fibrate-statin combination therapy	statin monotherapy	Relative (95% CI)	Absolute			
							All cause mortality (follow-up 48-92 weeks)						
							1	randomised trial	very serious ¹	no serious inconsistency	serious ¹	very serious ¹	reporting bias ¹
Vascular death - not measured													
0	-	-	-	-	-	none	-	-	-	-		CRITICAL	
Serious Adverse Events (follow-up 52 weeks)													
1	randomised trial	very serious ²	no serious inconsistency	serious ²	very serious ²	reporting bias ²	0/25 (0%)	0/23 (0%)	-	-	VERY LOW	CRITICAL	
Participants reaching ATPIII LDL-c goals (follow-up 24 weeks)													
1	randomised trial	very serious ³	no serious inconsistency	serious ³	no serious imprecision	reporting bias ³	39/40 (97.5%)	32/40 (80%)	OR 9.75 (1.16 to 82.11)	1000 more per 1000 (from 84 more to 1000 more)	VERY LOW	IMPORTANT	

1 Single 48-92 week trial same dose of pravastatin in both arms, reported no deaths.¹⁸⁸ The study described an unclear allocation concealment, unclear double-blind procedure and no intention-to-treat analysis was reported.¹⁸⁸

2 Single 52 week trial comparing same dose of fluvastatin in both arms, reported no SAEs.¹²³ The study described an unclear allocation concealment, unclear double-blind procedure and performed an intention-to-treat analysis.¹²³

3 Single 24 week trial comparing same dose of atorvastatin in both arms was included.¹⁶¹ The study described an unclear allocation concealment, unclear double-blind procedure and performed an intention-to-treat analysis.¹⁶¹

Table H-16. GRADE - Fibrate-statin combination therapy versus statin monotherapy in all participants

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	any statins plus fibrates	statins monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 12-92 weeks)												
3	randomised trial	very serious ¹	Serious ^{1,2}	Serious ^{1,2}	very serious ³	reporting bias ⁴	1/202 (0.5%)	2/137 (1.5%)	OR 0.28 (0.03 to 2.97) ⁵	11 fewer per 1000 (from 15 fewer to 28 more)	VERY LOW	CRITICAL
Vascular death - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Serious Adverse Events (follow-up 12-52 weeks)												
2	randomised trial	serious ⁶	serious ^{6,7}	serious ⁶	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	very serious ⁸	very serious ^{8,9,10}	serious ⁸	very serious ¹⁰	reporting bias ¹¹	124/153 (81%)	75/90 (83.3%)	not pooled	not pooled	VERY LOW	IMPORTANT

1 Three 12-92 week trials comparing different statins and different statin doses were included,^{125,134,188} one trial reported no deaths.¹⁸⁸ All trials described an unclear allocation concealment and did not perform intention-to-treat analysis, one trial described an appropriate double-blind procedure.¹³⁴

2 Participants in two trials diagnosed with hypercholesterolemia and DM.^{125,188} No specific risk reported in a third trial.¹³⁴

3 Wide confidence intervals (individual trials and pooled data).

4 Only 3 out of 11 included trials provided data on all cause mortality

5 Peto OR

6 Two trials comparing different statins and different statin doses were included,^{120,123} but one reported no serious adverse events.¹²³ One trial reported an adequate allocation concealment,¹²⁰ and one trial reported and appropriate double-blind procedure and performed an intention-to-treat analysis.¹²³

7 Data analyzed for a single study on which participants had hypercholesterolemia.¹²⁰

8 Two trials comparing different statins and different statin doses were included,^{125,161} none reported adequate allocation concealment or an appropriate double-blind procedure, one reported intention-to-treat analyses.¹⁶¹

9 All participants in both trials had diabetes mellitus.^{125,161}

10 Results based on two short-term trials, with significant heterogeneity (I-squared = 84%)

11 Results provided in only two out of 11 included trials

GRADE: Niacin-Statin Combination Therapy Compared With Statin Monotherapy

Table H-17. GRADE: Niacin-statin combination therapy versus statin monotherapy in participants requiring intensive lipid-lowering therapy

Quality assessment							Summary of findings					Quality	Importance
							No of patients		Effect				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Niacin-statin combination therapy	statin monotherapy	Relative (95% CI)	Absolute			
All cause mortality (follow-up 52 weeks)													
1	randomised trial	very serious ¹	no serious inconsistency ²	serious ¹	very serious ¹	reporting bias ¹	2/78 (2.6%)	1/71 (1.4%)	OR 1.84 (0.16 to 20.76)	11 more per 1000 (from 12 fewer to 215 more)	VERY LOW	CRITICAL	
Vascular death (follow-up 12 weeks)													
1	randomised trial	very serious ³	no serious inconsistency ²	serious ³	very serious ³	reporting bias ³	0/27 (0%)	0/27 (0%)	-	-	VERY LOW	CRITICAL	
Participants reaching ATPIII LDL-c goals (follow-up 16 weeks)													
1	randomised trial	very serious ⁴	no serious inconsistency	serious ⁴	very serious ⁵	reporting bias ⁴	21/32 (65.6%)	19/34 (55.9%)	OR 1.51 (0.56 to 4.08)	185 more per 1000 (from 205 fewer to 699 more)	VERY LOW	IMPORTANT	

1 Single study comparing mixed statins in both arms, with adequate allocation concealment and double-blind procedure, no intention-to-treat analysis reported, long-term follow-up, and 3 deaths¹⁹⁶

2 All participants had established vascular diseases

3 Single study comparing mixed statins in both arms, with unclear allocation concealment and double-blind procedure, no intention-to-treat analysis reported, short-term follow-up, and reporting no deaths¹⁹⁷

4 One 16 week trial comparing different statins and different doses was included.⁴⁹ This trial described an unclear allocation concealment, unclear double-blind procedure, and no intention-to-treat analysis.⁴⁹

5 Wide confidence interval.

Table H-18. GRADE: Niacin-statin combination therapy versus statin monotherapy in participants with established vascular disease

Quality assessment							Summary of findings					Quality	Importance
							No of patients		Effect				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Niacin-statin combination therapy	statin monotherapy	Relative (95% CI)	Absolute			
All cause mortality (follow-up 52 weeks)													
1	randomised trial	no serious limitations ¹	no serious inconsistency	serious ¹	very serious ¹	reporting bias ¹	2/78 (2.6%)	1/71 (1.4%)	OR 1.84 (0.16 to 20.76)	11 more per 1000 (from 12 fewer to 215 more)	VERY LOW	CRITICAL	
Vascular death (follow-up 12 weeks)													
1	randomised trial	very serious ²	no serious inconsistency	serious ²	very serious ²	reporting bias ²	0/27 (0%)	0/27 (0%)	-	-	VERY LOW	CRITICAL	
Participants reaching ATPIII LDL-c goals (follow-up 16 weeks)													
1	randomised trial	very serious ³	no serious inconsistency	serious ³	very serious ⁴	reporting bias ³	21/32 (65.6%)	19/34 (55.9%)	OR 1.51 (0.56 to 4.08)	185 more per 1000 (from 205 fewer to 699 more)	VERY LOW	IMPORTANT	

1 One 52 week trial comparing mixed statins in both arms, reported 3 deaths.¹⁹⁶ The trial reported an adequate allocation concealment and appropriate double-blind procedure, and did not perform an intention-to-treat analysis.¹⁹⁶

2 One 12 week trial comparing mixed statins in both arms, with unclear allocation concealment, unclear double-blind procedure, and no description of intention-to-treat analysis reported no vascular death.¹⁹⁷

3 One 16 week trial comparing different statins and different doses was included.⁴⁹ This trial described an unclear allocation concealment, unclear double-blind procedure, and no intention-to-treat analysis.⁴⁹

4 Wide confidence interval.

Table H-19. GRADE : Niacin-statin combination therapy versus statin monotherapy in all participants followed for more than 24 weeks

Quality assessment							Summary of findings					Quality	Importance
							No of patients		Effect				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Niacin-Statins combination therapy	statin monotherapy	Relative (95% CI)	Absolute			
All cause mortality (follow-up 24-52 weeks)													
4	randomised trial	serious ¹	serious ^{1,2}	serious ¹	serious ³	reporting bias ¹	3/595 (0.5%)	2/365 (0.5%)	OR 1.08 (0.17 to 6.72)	0 more per 1000 (from -4 fewer to 28 more)	VERY LOW	CRITICAL	
Vascular death (followup 28 weeks)													
1	randomised trial	very serious ⁴	no serious inconsistency	serious ⁴	very serious ^{4,3}	reporting bias ⁴	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 24-28 weeks)													
3	randomised trial	serious ⁵	serious ⁵	serious ⁵	serious ³	reporting bias ⁵	6/517 (1.2%)	3/294 (1%)	OR 1.00 (0.26 to 3.86)	0 fewer per 1000 (from 7 fewer to 28 more)	VERY LOW	CRITICAL	
Participants reaching ATPIII LDL-c goals - not measured													
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT	

1 Four 24-52 week trials comparing different statins and different statin doses reported this outcome.^{105,150,171,196} Three trials reported an adequate allocation concealment,^{105,171,196} two had an appropriate double-blind procedure,^{105,196} and intention-to-treat analysis was not performed.

2 In one study participants were diagnosed with coronary artery disease and LDL-c < 130 mg/dL,¹⁹⁶ participants in the second trial had hyperlipidemia and were statin naive.¹⁰⁵

3 Wide confidence interval.

4 One included trial comparing same dose of lovastatin in both arms, reported an unclear allocation concealment, an appropriate double-blind procedure and performed intention-to-treat analysis.¹²⁸

5 Three 24-28 week trials comparing different statins and different statin doses reported 9 SAEs during follow up.^{105,150,171} Two trials described an adequate allocation concealment and an appropriate double-blind procedure,^{105,171} none of the trials performed an intention-to-treat analysis.

Table H-20. GRADE: Niacin -statin combination therapy versus statin monotherapy in all participants

Quality assessment							Summary of findings					Quality	Importance
							No of patients		Effect				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Niacin-statin combination therapy	statin monotherapy	Relative (95% CI)	Absolute			
All cause mortality (follow-up 17-52 weeks ¹)													
6	randomised trial	serious ^{1,2}	serious ²	serious ²	very serious ²	reporting bias ²	3/755 (0.4%)	2/458 (0.4%)	OR 1.08 (0.17 to 6.72)	0 more per 1000 (from 3 fewer to 22 more)	VERY LOW	CRITICAL	
Vascular death (follow-up 12-28 weeks)													
2	randomised trial	serious ³	serious ³	serious ³	very serious ^{3,4}	reporting bias ³	1/141 (0.7%)	1/88 (1.1%)	OR 0.53 (0.03 to 8.64)	5 fewer per 1000 (from 11 fewer to 77 more)	VERY LOW	CRITICAL	
Serious Adverse Events (all trials) (follow-up 17-28 weeks)													
5	randomised trial	serious ⁵	serious ^{5,6}	serious ^{5,6}	serious ⁴	reporting bias ⁵	12/677 (1.8%)	4/387 (1%)	OR 1.29 (0.44 to 3.80)	3 more per 1000 (from 6 fewer to 27 more)	VERY LOW	CRITICAL	
Participants reaching ATPIII LDL-c goals (follow-up mean 16 weeks)													
1	randomised trial	very serious ⁷	very serious ^{7,8}	serious ^{7,8}	very serious ^{7,8}	reporting bias ⁷	78/105 (74.3%)	78/117 (66.7%)	not pooled	not pooled	VERY LOW	IMPORTANT	

1 Only the two long-term studies contributed data to the pooled analysis.^{105,196}

2 Six 17-52 week trials comparing different statins and different statin doses reported this outcome.^{104,105,150,170,171,196} Four reported no events.^{104,150,170,171} Two long-term trials reported 5 deaths.^{105,196} Four trials described an adequate allocation concealment,^{104,105,171,196} 3 reported an appropriate double-blind procedure,^{104,105,196} and none performed intention-to-treat analysis.

3 Two trials comparing different statins and different statin doses were included,^{128,197} one trial reported no vascular death.¹⁹⁷ Both trials reported an unclear allocation concealment, one long-term trial reported an appropriate double-blind procedure and performed intention-to-treat analysis.¹²⁸

4 Wide confidence interval.

5 Five 17-28 week trials comparing different statins and different statin doses were included.^{104,105,150,171,260} Three trials described an adequate allocation concealment, adequate double-blind procedure,^{104,105,171} no trial performed an intention-to-treat analysis.

6 Participants with mixed risk.

7 One 16 week trial was included.⁴⁹ This trial described an unclear allocation concealment, unclear double-blind procedure, and no intention-to-treat analysis.⁴⁹

8 Data is provided in four arms of the same trial comparing different statins and different statin doses in combination and monotherapy, but data was not pooled because of with significant heterogeneity (I-squared = 63%)

GRADE: BAS Plus Statin Therapy Compared With Statin Monotherapy

Table H-21. GRADE: BAS-statin combination 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	BAS-statin combination therapy	statin 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 targets (follow-up 12 weeks)												
1	randomised trial	very serious ¹	no serious inconsistency	serious ¹	no serious imprecision	reporting bias ¹	13/28 (46.4%)	5/31 (16.1%)	OR 4.51 (1.34 to 15.1)	348 more per 1000 (from 46 more to 734 more)	VERY LOW	IMPORTANT

¹ One trial comparing same dose of pravastatin in both arms was included. The trial reported unclear allocation concealment, no double-blind, no intention-to-treat analysis; short-term follow-up, and small sample size.¹⁰⁸ All participants on the trial required lipid lowering therapy because of established vascular diseases.

Table H-22. GRADE: BAS-statin combination therapy versus statin monotherapy in all participants followed for more than 24 weeks

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	BAS-statin combination therapy	statin monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 24 weeks)												
1	randomised trial	very serious ¹	no serious inconsistency	serious ¹	very serious ¹	reporting bias ¹	0/73 (0%)	1/77 (1.3%)	OR 0.35 (0.01 to 8.9)	8 fewer per 1000 (from 51 fewer to 119 more)	VERY LOW	CRITICAL
Vascular death - not measured												
0	-	-	-	-	-	None	-	-	-	-		CRITICAL
Serious Adverse Events (follow-up 30 weeks)												
1	randomised trial	very serious ²	no serious inconsistency	serious ²	very serious ²	reporting bias ²	1/44 (2.3%)	5/92 (5.4%)	OR 0.40 (0.05 to 3.6)	32 fewer per 1000 (from 51 fewer to 119 more)	VERY LOW	CRITICAL
Participants reaching ATP III LDL-c targets - not measured												
0	-	-	-	-	-	None	-	-	-	-		IMPORTANT

1 One 24 week trial comparing same dose of fluvastatin in both arms, reported one death.⁵² This trial described an unclear allocation concealment, unclear double-blind procedure and no intention-to-treat analysis was performed.⁵²

2 One 30 week trial comparing different statins reported six SAEs.¹⁹⁸ This trial described an unclear allocation concealment, unclear double-blind procedure and no intention-to-treat analysis was performed.¹⁹⁸

Table H-23. GRADE: BAS-statin combination therapy versus statin monotherapy in all participants

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	BAS-statin combination therapy	statin monotherapy	Relative (95% CI)	Absolute		
All cause mortality (follow-up 4-24 weeks)												
3	randomised trial	very serious ¹	serious ¹	serious ¹	very serious ²	reporting bias ¹	1/195 (0.5%)	1/178 (0.6%)	OR 1.07 (0.11 to 10.51)	0 more per 1000 (from -5 fewer to 54 more)	VERY LOW	CRITICAL
Vascular death - not measured												
0	-	-	-	-	-	None	-	-	-	-		CRITICAL
Serious Adverse Events (follow-up 6-30 weeks)												
2	randomised trial	serious ³	serious ³	serious ³	very serious ³	reporting bias ^{3,4}	1/112 (0.9%)	6/166 (3.6%)	OR 0.39 (0.06 to 2.36)	22 fewer per 1000 (from 34 fewer to 45 more)	VERY LOW	CRITICAL
Participants reaching ATPIII LDL-c goals (follow-up 12 weeks)												
1	randomised trial	very serious ⁵	no serious inconsistency	serious ⁵	no serious imprecision	reporting bias ⁴	13/28 (46.4%)	5/31 (16.1%)	OR 4.51 (1.34 to 15.1)	348 more per 1000 (from 46 more to 734 more)	VERY LOW	IMPORTANT

1 Three trials comparing different statins and different statin doses were included.^{52,172,185} One trial reported no deaths during a 4 week follow up of 76 participants,¹⁸⁵ and a single long term trial reported one death.⁵² One trial described adequate allocation concealment and appropriate double-blind procedure.¹⁷² None of the trials performed an intention-to-treat analysis.

2 Wide confidence interval.

3 Two 6-30 week trials comparing different statins and different statin doses reported 7 SAEs.^{172,198} One reported appropriate allocation concealment and appropriate double-blind procedure.¹⁷² None reported intention-to-treat analysis.

4 Results provided in only one out of 17 included trials

5 One trial comparing same dose of pravastatin in both arms was included. The trial reported unclear allocation concealment, no double-blind, no intention-to-treat analysis; short-term follow-up, and small sample size.¹⁰⁸ All participants on the trial required lipid lowering therapy because of established vascular diseases.

GRADE: Omega-3 Fatty Acid Plus Statin Therapy Compared With Statin Monotherapy

Table H-24. GRADE: statin plus Omega-3 therapy versus statin monotherapy, in all participants

Quality assessment							Summary of findings					Quality	Importance
							No of patients		Effect				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Omega-statin combination therapy	statin monotherapy	Relative (95% CI)	Absolute			
All cause mortality (follow-up 5-240 weeks)													
3	randomised trial	No serious limitations ¹	Serious ¹	Serious ¹	no serious imprecision	reporting bias ¹	286/9469 (3%)	265/9471 (2.8%)	OR 1.08 (0.91 to 1.28)	2 more per 1000 (from 2 fewer to 8 more)	VERY LOW	CRITICAL	
Vascular death - not measured													
0	-	-	-	-	-	none	-	-	-	-		CRITICAL	
Serious Adverse Events (follow-up 8 weeks)													
1	randomised trial	serious ²	no serious inconsistency	serious ²	very serious ^{2,3}	reporting bias ²	4/122 (3.3%)	1/132 (0.8%)	OR 4.44 (0.49 to 40.29)	27 more per 1000 (from 4 fewer to 238 more)	VERY LOW	CRITICAL	
Participants reaching ATPIII LDL-c goals - not measured													
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT	

1 Three 5-240 week trials comparing different statins and different statin doses were included,^{141,177,180} two short term trials reported no deaths.^{177,180} Two trials reported an adequate allocation concealment,^{141,180} two reported appropriate double-blind procedure,^{177,180} and one performed intention-to-treat analysis.¹⁴¹

2 One 8 week trial comparing same dose of simvastatin in both arms was included.¹⁸⁰ This trial described an adequate allocation concealment and appropriate double-blind procedure, no intention-to-treat analysis was reported.¹⁸⁰

3 Results based on a single-trial with wide confidence interval

Table H-25. GRADE: Omega-3-statin combination therapy versus statin monotherapy, in participants of Asian origin (long-term duration)

Quality assessment							Summary of findings					Quality	Importance
							No of patients		Effect				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Omega-statin combination therapy	statin monotherapy	Relative (95% CI)	Absolute			
All cause mortality (follow-up 240 weeks)													
1	randomised trial	no serious limitations ¹	no serious inconsistency	serious ¹	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 1000 (from 2 fewer to 8 more)	LOW	CRITICAL	
Vascular death - not measured													
0	-	-	-	-	-	none	-	-	-	-		CRITICAL	
Participants reaching ATPIII LDL-c goals - not measured													
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT	

¹ One long-term trial comparing mixed statins, with adequate allocation concealment and intention-to-treat analysis was described, no double-blind procedure reported.¹⁴¹ All participants in the trial were of Asian origin.

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Appendix J: Peer Reviewers

The UO-EPC gratefully acknowledges the following individuals who reviewed the initial draft of this evidence report, and provided constructive feedback. Acknowledgement does not reflect endorsement of this report.

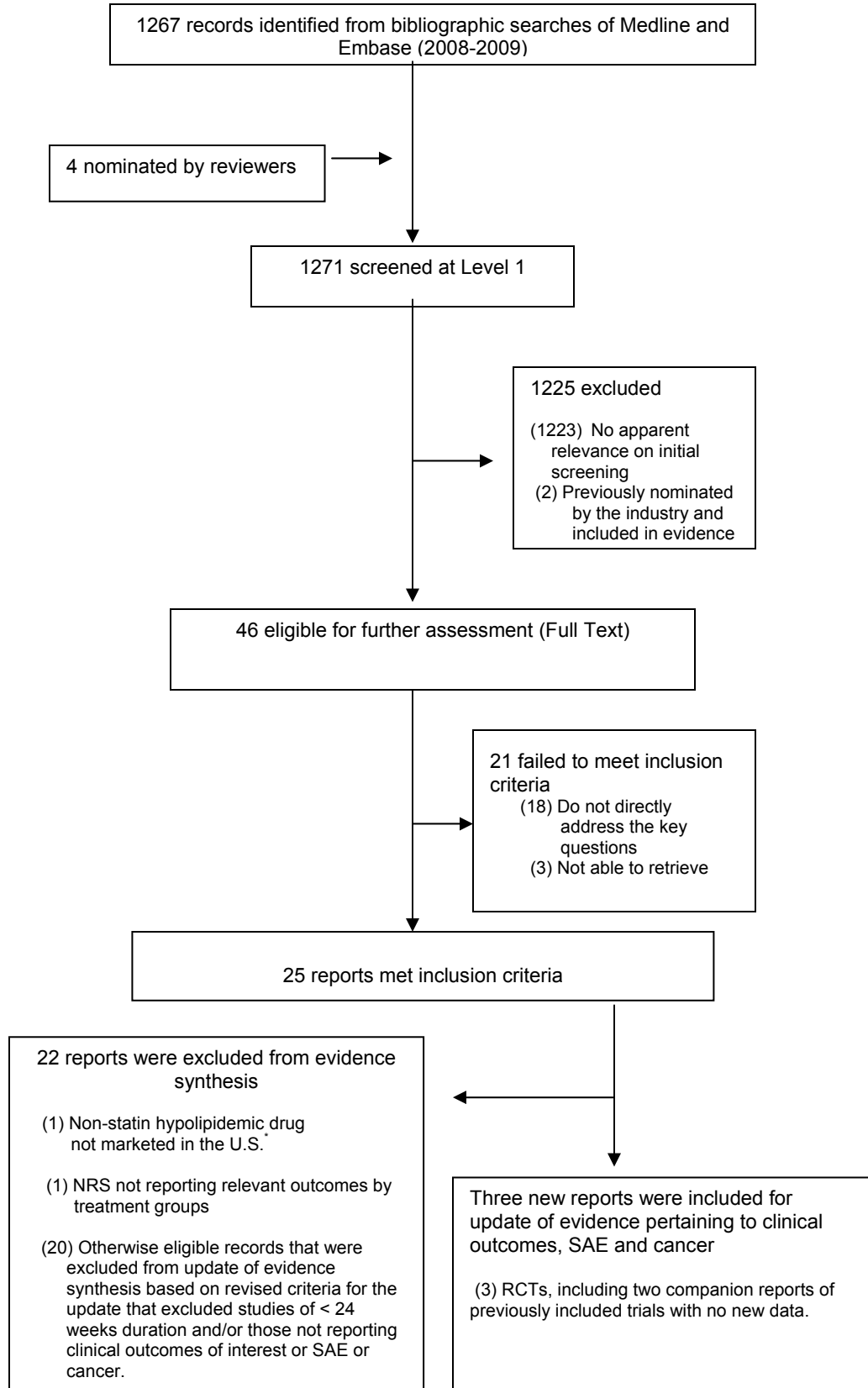
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Appendix K: Literature Search 2009 Update (August 2008 to May 2009) Including the Update Flow Chart and List of Included and Excluded Records

Flow Chart



Included Studies

Airan-Javia SL, Wolf RL, Wolfe ML, et al. Atheroprotective lipoprotein effects of a niacin-simvastatin combination compared to low- and high-dose simvastatin monotherapy. *Am Heart J* 2009 Apr;157(4):687-8.

Bays H, Sapre A, Taggart W, et al. Long-term (48-week) safety of ezetimibe 10 mg/day coadministered with simvastatin compared to simvastatin alone in patients with primary hypercholesterolemia. *Curr Med Res Opin* 2008 Oct;24(10):2953-66.

Saito Y, Yokoyama M, Origasa H, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis* 2008 Sep;200(1):135-40.

Excluded Studies – Full Text Relevance

Do Not Directly Address the Key Questions

Farmer JA. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis (the SEAS trial). *Curr Atheroscler Rep* 2009 Mar;11(2):82-3.

Maccubbin D, Bays HE, Olsson AG, et al. Lipid-modifying efficacy and tolerability of extended-release niacin/laropirant in patients with primary hypercholesterolaemia or mixed dyslipidaemia. *Int J Clin Pract* 2008 Dec;62(12):1959-70.

Bays HE, Maccubbin D, Meehan AG, et al. Blood pressure-lowering effects of extended-release niacin alone and extended-release niacin/laropirant combination: a post hoc analysis of a 24-week, placebo-controlled trial in dyslipidemic patients. *Clin Ther* 2009 Jan;31(1):115-22.

Valdivielso P, Rioja J, Garcia-Arias C, et al. Omega 3 fatty acids induce a marked reduction of apolipoprotein B48 when added to fluvastatin in patients with type 2 diabetes and mixed hyperlipidemia: a preliminary report. *Cardiovasc* 2009;8:1

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Di SM, Morelli G, Doyle RT, et al. Effect of omega-3-acid ethyl esters on steady-state plasma pharmacokinetics of atorvastatin in healthy adults. *Expert Opin Pharmacother* 2008 Dec;9(17):2939-45.

Maki KC, McKenney JM, Reeves MS, et al. Effects of adding prescription omega-3 acid ethyl esters to simvastatin (20 mg/day) on lipids and lipoprotein particles in men and women with mixed dyslipidemia [erratum appears in *Am J Cardiol* 2008 Nov 15;102(10):1425]. *Am J Cardiol* 2008 Aug 15;102(4):429-33.

Domanski M, Tian X, Fleg J, et al. Pleiotropic effect of lovastatin, with and without cholestyramine, in the post coronary artery bypass graft (Post CABG) trial. *Am J Cardiol* 2008 Oct 15;102(8):1023-7.

Ara R, Pandor A, Tumor I, et al. Estimating the health benefits and costs associated with ezetimibe coadministered with statin therapy compared with higher dose statin monotherapy in patients with established cardiovascular disease: results of a Markov model for UK costs using data registries. *Clin Ther* 2008 Aug;30(8):1508-23.

Berthold HK, Laaksonen R, Lehtimäki T, et al. SREBP-1c gene polymorphism is associated with increased inhibition of cholesterol-absorption in response to ezetimibe treatment. *Exp Clin Endocrinol Diabetes* 2008 May;116(5):262-7.

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de Rojas FD, De FT, Ponte A, et al. Coronary heart disease and dyslipidemia: A cross-sectional evaluation of prevalence, current treatment, and clinical control in a large cohort of Spanish high-risk patients: The

PRINCEPS study. *Prev Cardiol* 2009;12(2):65-71.

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Maki KC, Lubin BC, Reeves MS, et al. Prescription omega-3 acid ethyl esters plus simvastatin 20 and 80 mg: effects in mixed dyslipidemia. *Journal of Clinical Lipidology* 2009;3(1):33-8.

Block JP. Limited benefit for aggressive lipid lowering with simvastatin/ezetimibe in patients with aortic stenosis; possible increased risk of cancer. *Journal of Clinical Outcomes Management* 2008;15(11):528+530

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Not Able To Retrieve

Hari KS, Rajeev E, Tharakan JA, et al. Efficacy and safety of combination of extended release niacin and atorvastatin in patients with low levels of high density lipoprotein cholesterol. *Indian Heart J* 2008 May;60(3):215-22.

Banerjee AK. Changing face of dyslipidemia therapy. *Indian Heart Journal* 2008;60(3):192-4.

Schmitz SA, O'Regan DP, Fitzpatrick J, et al. Quantitative 3T MR imaging of the descending thoracic aorta: patients with familial hypercholesterolemia have an increased aortic plaque burden despite long-term lipid-lowering therapy. *J Vasc Interv Radiol* 2008 Oct;19(10):1403-8.

Excluded Studies - Evidence Synthesis

Non-Randomized Studies

Derosa G, D'Angelo A, Franzetti IG, et al. Efficacy and safety of ezetimibe/simvastatin association on non-diabetic and diabetic patients with polygenic hypercholesterolemia or

combined hyperlipidemia and previously intolerant to standard statin treatment. *Journal of Clinical Pharmacy and Therapeutics* 2009;34(3):267-76.

Drug(s) Not Marketed in the United States

Nomura S, Inami N, Shouzu A, et al. The effects of pitavastatin, eicosapentaenoic acid and combined therapy on platelet-derived

microparticles and adiponectin in hyperlipidemic, diabetic patients. *Platelets* 2009 Feb;20(1):16-22.

Otherwise Eligible Records Identified in Search Update That Were Excluded from Evidence Syntheses Because Did Not Report Clinical Outcomes or Because < 24 Weeks Duration

Mindrescu C, Gupta RP, Hermance EV, et al. Omega-3 fatty acids plus rosuvastatin improves endothelial function in South Asians with dyslipidemia. *Vasc Health Risk Manag* 2008;4(6):1439-47.

Zhu T, Awni WM, Hosmane B, et al. ABT-335, the choline salt of fenofibric acid, does not have a clinically significant pharmacokinetic interaction with rosuvastatin in humans. *J Clin Pharmacol* 2009 Jan;49(1):63-71.

Goldberg AC, Bays HE, Ballantyne CM, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with atorvastatin in patients with mixed dyslipidemia. *Am J Cardiol* 2009 Feb 15;103(4):515-22.

Liu PY, Liu YW, Lin LJ, et al. Evidence for statin pleiotropy in humans: differential effects of statins and ezetimibe on rho-associated coiled-coil containing protein kinase activity, endothelial function, and inflammation. *Circulation* 2009 Jan 6;119(1):131-8.

Malmstrom RE, Settergren M, Bohm F, et al. No effect of lipid lowering on platelet activity in patients with coronary artery disease and type 2 diabetes or impaired glucose tolerance. *Thromb Haemost* 2009 Jan;101(1):157-64.

Lin TH, Voon WC, Yen HW, et al. Randomized comparative study of the effects of treatment with once-daily, niacin extended-release/lovastatin and with simvastatin on lipid profile and fibrinolytic parameters in Taiwan.

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Zubaid M, Shakir DK, Bazargani N, et al. Effect of ezetimibe coadministration with simvastatin in a Middle Eastern population: a prospective, multicentre, randomized, double-blind, placebo-controlled trial. *J Cardiovasc Med (Hagerstown)* 2008 Jul;9(7):688-93.

Jones PH, Davidson MH, Kashyap ML, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with rosuvastatin in patients with mixed dyslipidemia: A phase 3 study. *Atherosclerosis* 2009;204(1):208-15.

Farnier M, Aversa M, Missault L, et al. Lipid-altering efficacy of ezetimibe/simvastatin 10/20 mg compared with rosuvastatin 10 mg in high-risk hypercholesterolaemic patients inadequately controlled with prior statin monotherapy - The IN-CROSS study. *Int J Clin Pract* 2009;63(4):547-59.

Insull J, W, Basile JN, et al. Efficacy and safety of combination therapy with niacin extended-release and simvastatin versus atorvastatin in patients with dyslipidemia: The SUPREME Study. *Journal of Clinical Lipidology* 2009;3(2):109-18.

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