Drug Class Review
on
HMG-CoA Reductase Inhibitors (Statins)

Final Report Update 4 Evidence Tables

August 2006

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Update 2 Report Date: June 2004
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A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Upon review of the last scan, the Drug Effectiveness Review Project governance group elected not to proceed with another full update of this report. Some portions of the report may not be up to date. Prior versions of this report can be accessed at the DERP website.

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Evidence Tables

Highlighting indicates new evidence.

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Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
	Atorvastatin vs. Lovastatin		
Davidson et al. 1997 R (3:1), DB, MC, PC, not ITT 1,049 patients randomized (n= 789 atorva, 260 lova) 52 weeks Parke-Davis Pharmaceuticals	Men and women 18-80 years with LDL ≥160 mg/dl and ≥145 mg/dl after 2 weeks dietary phase. Mean baseline LDL-c 189-192 mg/dl	NCEP step 1 diet and atorva 10 mg qd or lova 20 mg qd for 52 weeks; or placebo for 16 weeks, then atorva 10 mg qd or lova 20 mg qd for 36 weeks. Doses doubled at 22 weeks if LDL-c goals (based upon their risk factors) not achieved.	Efficacy analysis for 970 patients. **LDL-c reduction from baseline at week 16:** atorva 10 mg: 36% lova 20 mg: 27% placebo unchanged (p<0.05 vs. lova or placebo) **LDL-c reduction from baseline at week 52:** atorva: 37% (27% had dose doubled) lova: 29% (49% had dose doubled) (p<0.05 vs. lovastatin) **HDL at week 16:** atorva and lova both increased 7% (p NS) **HDL at week 52:** atorva and lova both increased 7% (p NS) **Trigs:** atorva reduction 16%; lova reduction 8% (p<0.05) **Achieved LDL-c goal:** atorva 78% vs. lova 63%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Davidson et al. 1997 R (3:1), DB, MC, PC, not ITT 1,049 patients randomized (n= 789 atorva, 260 lova) 52 weeks Parke-Davis Pharmaceuticals	Adverse drug events (ADEs) similar across groups. Only those ADEs occurring ≥2% were reported. Withdrawal due to ADEs occurred in 3% of atorva vs. 4% of lova patients; 8% of atorva vs. 7% of lova patients had a serious ADE (no details provided), including 1 patient developing pancreatitis in atorva group. Elevation in ALT >3x ULN occurred in 1 (0.1%) atorva, 3 (1.2%) lova, and 1 (0.7%) placebo patients. No patient experienced an increase in creatine kinase (CK) of >10 times ULN. Equivalent doses not compared.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
	Atorvastatin vs. Pravastatin		
Bertolini et al. 1997 R (3:1), DB, MC, not ITT 305 patients randomized (n= 227 atorva, 78 prava) 1 year 2 authors employed by Parke-Davis Pharmaceuticals.	Men and women 18-80 years with LDL-c 160-250 mg/dl. Mean baseline LDL-c 195 mg/dl	6 week dietary phase NCEP step 1 diet and atorva 10 mg qd or prava 20 mg qd. If LDL-c remained ≥130 mg/dl at weeks 4 and 10, doses were doubled at week 16.	Efficacy analysis for 299 patients **LDL-c reduction from baseline at week 16:** atorva 10 mg: 35% prava 20 mg: 23% (p≤0.05) **LDL-c reduction from baseline at week 52:** atorva: 35% (24% had dose doubled) prava: 23% (64% had dose doubled) (p≤0.05). **HDL:** atorva increased 7%, prava increased 10% (NS) **Trigs:** atorva reduction 14%, prava reduction 3% (p≤0.05). **Achieved LDL-c goal:** atorva 71% vs. prava 26%
Assman et al. 1999 R (3:1), DB, MC, not ITT 297 patients randomized (n= 224 atorva, 73 prava) 52 weeks 2 authors employed by Parke-Davis Pharmaceuticals.	Men or women 18-80 years with an LDL-c 160-250 mg/dl during dietary phase. Mean baseline LDL-c 201 mg/dl.	6-week dietary and placebo phase. NCEP step 1 diet. Mild to moderate CHD risk (dose level 1: LDL-c goal <130 mg/dl): 10 mg qd atorva (n=145) vs. prava 20 mg qd (n=27). Severe CHD risk (dose level 2: LDL-c goal <115 mg/dl): atorva 20 mg qd (n=79) vs. prava 40 mg qd (n=46). If goal not reached, dose doubled at week 4, and again at week 8 and week 16. Maximum doses: atorva 80 mg qd, prava 40 mg qd.	Efficacy analysis for 279 patients. **LDL-c reduction from baseline at 1 year:** atorva: 39% (p< 0.05) prava: 29% **HDL:** atorva increased 7% prava increased 9% (NS) **Trigs:** atorva reduction 13% (p<0.05) prava reduction 8% **Achieved LDL-c goal at last visit:** atorva\= 51% vs. prava 20% (p=0.0001) 35% atorva (20 mg-17%, 40 mg-12%, 80 mg-5%) vs. 88% prava (40 mg-88%) patients had doses doubled at least once.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Bertolini et al. 1997 R (3:1), DB, MC, not ITT 305 patients randomized (n= 227 atorva, 78 prava) 1 year 2 authors employed by Parke-Davis Pharmaceuticals.	Severe adverse drug events (ADEs) similar for atorva (7%) and prava (9%); 7 patients in the atorva and 2 in the prava group withdrawn from study as a result of a severe ADE (no details). No patient in either group had clinically important elevations in AST, ALT or CK. Equivalent doses not compared.
Assman et al. 1999 R (3:1), DB, MC, not ITT 297 patients randomized (n= 224 atorva, 73 prava) 52 weeks 2 authors employed by Parke-Davis Pharmaceuticals.	9 patients (4%) in atorva group withdrew as a result of ADEs vs. 2 patients (3%) in prava group. 2 patients receiving atorva (unknown dose) experienced an elevation in ALT >3 X upper limit of normal. No patient on prava experienced an elevation. Most commonly reported ADE with atorva was myalgia and rash each reported by 4 patients. Most common ADE with prava was arthralgia in 2 patients. (unknown doses) 35% of atorva vs. 63% of prava patients categorized in the severe CHD risk or dose level II. Equivalent doses not compared.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Nissen et al, 2004 R, DB, MC, PC 657 patients randomized 18 months Funded by Pfizer	Men and women aged 30 to 75 years who required coronary angiography for a clinical indication and demonstrated at least 1 obstruction with angiographic luminal diameter narrowing of 20% or more. Lipid criteria required an LDL-c level between 125 mg/dL and 210 mg/dL after 4 to 10 week washout period. Mean baseline LDL-c atorva 80mg: 150.2	Atorva 80 mg daily or prava 40 mg daily.	Efficacy analysis on 502 patients. LDL-c reduction from baseline at 18 months: Atorva 80 mg: 46.3% (p<0.001) Prava 40 mg: 25.2% HDL-c increase from baseline at 18 months: Atorva 80 mg: 2.9% Prava 40 mg: 5.6% (p=0.06) Trigs reduction from baseline at 18 months: Atorva 80 mg: 20.0% (p<0.001) Prava 40 mg: 6.8%
Saklamaz et al, 2005 R, single center, blinding not reported 21 patients randomized 8 weeks treatment Funding not reported	Men and women (mean age 51.7±9.1 years) with type IIa and IIb hyperlipidemia. Mean baseline LDL-c pravastatin: 186±36 mg/dL atorvastatin: 174±10 mg/dL	pravastatin 20 mg or atorvastatin 10 mg or fenofibrate 250 mg	**% LDL-c reduction from baseline at 12 weeks:** pravastatin 20: 24.2% atorvastatin 10: 40.2% **% HDL-c increase from baseline at 12 weeks:** pravastatin 20: 3.4% atorvastatin 10: 9.8% **% trig reduction from baseline at 12 weeks:** pravastatin 20: 24.3% atorvastatin 10: 20.1%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Nissen et al, 2004 R, DB, MC, PC 657 patients randomized 18 months Funded by Pfizer	6.7% of prava and 6.4% of atorva group discontinued drug for adverse events. Most common reason was musculoskeletal complaints (3.4% prava, 2.8% atorva). Equivalent doses not compared
Saklamaz et al, 2005 R, single center, blinding not reported 21 patients randomized 8 weeks treatment Funding not reported	Adverse events not reported.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
	Atorvastatin vs. Simvastatin		
Bays et al., 2005 R, Open-label, multicenter 315 patients randomized (n=82 atorvastatin, 76 simvastatin, 157 niacin ER plus lovastatin) 16 weeks treatment Funded by Kos Pharmaceuticals	Men and women with elevated LDL-c (>=160mg/dL, or, if coronary heart disease was present, >=130 mg/dL) and low HDL-c (<45 mg/dL for men and <50 mg/dL for women). Mean baseline LDL-c 194 mg/dL	6-week screening phase during which lipid modifying drugs were discontinued, then treatment for the first 8 weeks: atorvastatin 10 mg or simvastatin 10 mg At week 8, dose increased for 4 weeks: atorvastatin 20 mg or simvastatin 20 mg At week 12, dose increased for 4 weeks: atorvastatin 40 mg or simvastatin 40 mg	% LDL-c reduction from baseline at 8, 12, and 16 weeks (p vs atorva): atorva 10/20/40: 38% (p<0.05)/45% (p<0.05)/49% (p<0.05) simva 10/20/40: 28%/35%/39% % HDL-c increase from baseline at 8, 12, and 16 weeks (p vs atorva): atorva 10/20/40: 3% (p<0.05)/4% (p<0.05)/6% (p<0.05) simva 10/20/40: 7%/8%/7% % trig reduction from baseline at 8, 12, and 16 weeks (p vs atorva): atorva 10/20/40: 20%/30% (p<0.05)/31% (p<0.05) simva 10/20/40: 18%/15%/19%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Bays et al., 2005 R, Open-label, multicenter 315 patients randomized (n=82 atorvastatin, 76 simvastatin, 157 niacin ER plus lovastatin) 16 weeks treatment Funded by Kos Pharmaceuticals	Adverse events not reported.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Dart A et al. 1997 R (3:1), DB, MC, not ITT 177 patients randomized (n= 132 atorvastatin, 45 simvastatin) 1 year Support and contribution by Parke-Davis Pharmaceutical Research Division	Men or women 18-80 years with an LDL-c 160-300 mg/dl during the dietary phase. Mean baseline LDL-c 208-214 mg/dl	6-week dietary and placebo phase. NCEP step 1 diet and atorvastatin 10 mg qd or simvastatin 10 mg qd. Doses were doubled at week 16 if LDL-c was not ≤ 130 mg/dl.	Efficacy analysis for 177 patients. **LDL-c reduction from baseline at week 16:** Atorvastatin 10 mg: 37% Simvastatin 10 mg: 30% (p<0.05) **LDL-c reduction from baseline at week 52:** Atorvastatin: 38% (48% had dose doubled) Simvastatin: 33% (62% had dose doubled) (p≤0.05) **HDL at week 16:** Atorvastatin increased 7% Simvastatin increased 7% (p NS) **HDL at week 52:** Atorvastatin increased 7% Simvastatin increased 7% (p NS) **Trigs:** Atorvastatin reduction 21% Simvastatin reduction 12% (p≤0.05) **Achieved LDL-c goal:** atorva 46% vs. simva 27%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Dart A et al. 1997 R (3:1), DB, MC, not ITT 177 patients randomized (n= 132 atorvastatin, 45 simvastatin) 1 year Support and contribution by Parke-Davis Pharmaceutical Research Division	No clinically significant changes in ALT, AST or CK in either group. No differences in percentages of reported ADE between groups. None of the serious ADEs in either group thought to be due to the statin. Most common ADE with atorvastatin was myalgia (3%). Most common ADE with simvastatin was arthralgia (7%) and chest pain (4%). 2 patients in each group withdrawn as a result of ADEs. Details only provided for 1 patient on atorvastatin who reported excessive sweating possibly related to treatment. No other details on ADEs provided. Equivalent doses not compared.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Crouse et al. 1999 R, OL, MC, not ITT 846 patients randomized 12 weeks Merck supported and participated in study.	Men or women Mean baseline LDL-c 212.7 mg/dl	4-week dietary run-in phase, then: atorva 20 mg qd (n=210) or atorva 40 mg qd (n=215) or simva 40 mg qd (n=202) or simva 80 mg qd (n=215)	*Efficacy analysis for 842 patients.* **LDL-c reduction from baseline at 12 weeks:** atorva 20 mg: 45% * atorva 40 mg: 51.1% simva 40 mg: 42.7% simva 80 mg: 49.2% (*p<0.05 atorva 20 vs. simva 40) **HDL-c increase from baseline at 12 weeks:** atorva 20 mg: 4% atorva 40 mg: 3% simva 40 mg: 6.7% * simva 80 mg: 6.6% * (*p<0.01 atorva vs. simva) **Trig reduction from baseline at 12 weeks:** atorva 20 mg: 23.3% atorva 40 mg: 29.6% * simva 40 mg: 23% simva 80 mg: 25.2% (*p<0.01 atorva 40 vs. simva 80)
Marz et al. 1999 R (2:1) OL, MC, not ITT 2,856 patients randomized (n= 1897 atorva, 959 simva) 14 weeks Sponsored by Parke-Davis and Pfizer	Men or women 35-75 years with CHD and LDL-c ≥130 mg/dl after the diet phase. Mean baseline LDL-c 186-188 mg/dl	6-week diet phase then atorva 10 mg qd or simva 10 mg qd. Doses were doubled at weeks 5 and/or 10 if LDL-c was ≥ 100 mg/dl.	Number of patients in efficacy analysis not specified. **LDL-c reduction from baseline at week 14:** atorva 10 mg: 37.6% simva 10 mg: 31.9% (p<0.001) **Overall LDL-c reduction:** 188-105 mg/dl in atorva vs. 186-112 mg/dl in simva group. (p<0.001) 38% atorva vs. 54% simva users increased to 40 mg qd.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Crouse et al. 1999 R, OL, MC, not ITT 846 patients randomized 12 weeks Merck supported and participated in study.	No safety data or details on patient population provided in this trial. Primary endpoint in this study was effects of atorva or simva on HDL and Apolipoprotein A-1. <u>Dose equivalence</u> Atorva 20 mg > or ≈ Simva 40 mg. Atorva 40 mg = Simva 80 mg
Marz et al. 1999 R (2:1) OL, MC, not ITT 2,856 patients randomized (n= 1897 atorva, 959 simva) 14 weeks Sponsored by Parke-Davis and Pfizer	ADEs were similar between groups occurring in 36.3% in the atorva vs. 35.7% in the simva group. Withdrawal due to ADE were similar between groups. Serious ADEs occurred in 2% atorva vs. 3% simva (NS). No differences in elevation in ALT or AST or CK during the trial between groups. <u>Dose equivalence</u> Atorvastatin 20 mg qd ≈ simvastatin 40 mg qd.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Paragh et al, 2004 R, OL, crossover, ITT not stated 49 patients randomized (50% to simvastatin and 50% to atorvastatin) 10 months (3 mos./drug) Industry role, if any, not specified	Men or women 25-70 years with Frederickson IIa and IIb hyperlipoproteinaemia with LDL-c >158 ml/dL and trigs <398 mg/dL. **Mean baseline LDL-c:** Simvastatin 20 mg: 182 mg/dL Atorvastatin 10 mg: 174 mg/dL	8-week NCEP Step 1 dietary run-in then randomized to simva 20 mg/d or atorv 10 mg/d for 3 months. Followed by 8-week washout period, then switched to alternate drug in corresponding dose for 3 months.	**% LDL-c reduced from baseline after 3 months:** Simva 20 mg: -18.5% Atora 10 mg: -28.9% (p<0.001 for baseline vs. 3 month levels; p<0.001 for simva vs. atorva) % **HDL-c increased from baseline after 3 months:** Simva 20 mg/d: +3.8% Atorva 10 mg/d: + 9.2% (p=not significant(n.s.) for baseline vs. 3 month levels; p=n.s. for simva vs.atorva) **% Trig level decreased from baseline after 3 months:** Simva 20 mg/d: -15.2 % Atorva 10 mg/d: -29.5% (p<0.01 for baseline vs. 3 month levels; p=n.s. for simva vs. atorva) **% patients reaching target LDL-c levels**: Simva 20 mg/d: 28% Atorva 10 mg/d: 44% (no p-values given)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Paragh et al, 2004 R, OL, crossover, ITT not stated 49 patients randomized (50% to simvastatin and 50% to atorvastatin) 10 months (3 mos./drug) Industry role, if any, not specified	No serious adverse events reported nor discussed in detail. No changes in physical examination findings or laboratory values occurred.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Van Dam et al. 2000 R, SB, MC, not ITT 378 patients randomized (n= 185 atorvastatin, 193 simvastatin) 8 weeks Supported by Parke-Davis and Pfizer Pharmaceuticals. One author employed by Parke-Davis.	Men or women 18-80 years currently treated with simvastatin 20 or 40 mg qd and LDL-c levels > 100 mg/dl. Mean baseline LDL-c Simvastatin 20 mg: 138 mg/dl Simvastatin 40 mg: 145 mg/dl	4-week simvastatin run-in phase followed by randomization as follows: Simvastatin 20 mg users: Atorvastatin 20 mg or simvastatin 20 mg. Simvastatin 40 mg users: Atorvastatin 40 mg or simvastatin 40mg	Efficacy analysis for 324 patients. **Additional reduction in LDL-c when switching from simvastatin to:** (p<0.05) Atorva 20 mg: 14± 14% Simva 20 mg: 3.3 ± 14%(p) Atorva 40 mg: 2.85 ±12.7% Simva 40 mg: 14.6 ± 15.2% (p) **HDL:** (p>0.05) Atorva 20 mg: reduction 1.41 ± 10.3% Simva 20 mg: increased 0.49 ± 10.8% Atorva 40 mg: reduction 1.07 ± 11.8% Simva 40 mg: increased 2.76 ± 10.4 **Trigs:** (p>0.05) Atorva 20 mg: reduction 10.9% ± 25% Simva 20 mg: reduction 4.21 ± 32.5% Atorva 40 mg: reduction 0.85 ± 36% Simva 40 mg: increased 8.4 ± 36.6% **Achieved NCEP LDL-c goal:** 28% atorva vs. 13% simva
Farnier et al. 2000 **R (2:1:2), OL, MC, ITT** 272 patients randomized (n= 109 atorvastatin, 163 simvastatin) 12 weeks Supported by grant from Parke-Davis.	Men or women 18-70 years with elevated LDL-c. Mean baseline LDL-c Atorvastatin 10 mg: 247 ± 45 mg/dl Simvastatin 10 mg: 242 ± 47 mg/dl Simvastatin 20 mg: 237 ± 39 mg/dl.	6-week placebo-dietary run-in phase then randomized to: Atorvastatin 10 mg, simvastatin 10 mg or simvastatin 20 mg qd for 6 weeks.	Efficacy analysis for 272 patients. **LDL-c reduction from baseline at 6 weeks:** Atorva 10 mg: 37% Simva 10 mg: 28.9% Simva 20 mg: 33.8% (90% CI 0.66-5.7 atorva 10 mg vs. simva 20 mg) **HDL:** (NS Atorva 10 mg vs. simva 20 mg) atorva 10 mg increased 5.7% simva 10 mg increased 2.2% simvastatin 20 mg increased 3% **Trigs:** (NS atorva 10 vs. simva 20) atorva 10 mg reduction 19.2% simva 10 mg reduction 4.6% simva 20 mg reduction 16%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Van Dam et al. 2000 R, SB, MC, not ITT 378 patients randomized (n= 185 atorvastatin, 193 simvastatin) 8 weeks Supported by Parke-Davis and Pfizer Pharmaceuticals. One author employed by Parke-Davis.	Total 71 ADEs for 54 of 185 atorva patients vs. total 39 ADEs for 32 of 193 simva patients (p=0.005). Although not much detail provided, most frequent ADEs were myalgia and headache. Myalgia was reported most commonly in atorva group. No mention if ADEs reported more often in the higher-dose groups. No reports of elevations in ALT, AST or CK during the study. Overall, HDL reduced 1.3% in atorva vs. increased 1.3% in simva group (p=0.04). Triglycerides reduced by 7.5% in atorva vs. increased 5.6% in simva group (p=0.005). <u>Equivalent doses not compared.</u>
Farnier et al. 2000 **R (2:1:2), OL, MC, ITT** 272 patients randomized (n= 109 atorvastatin, 163 simvastatin) 12 weeks Supported by grant from Parke-Davis.	Authors report no difference in incidence of ADEs between groups (atorva 10 mg = 11.9% vs. simva 10 mg =5.5% vs. simva 20 mg = 3.7%). Few details provided. One patient in atorva group had an increase in ALT >3x ULN. No elevation in CK reported. <u>Dose equivalence</u> atorvastatin 10 mg qd ≈ simva 20 mg qd

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Recto et al. 2000 R, OL, MC, crossover, not ITT 258 (?) patients (n= 125 atorva, 126 simva) 12 weeks Study supported by grant from Merck.	Men or women 21-70 years with an LDL-c ≥ 130 mg/dl and trigs ≤ 350 mg/dl. Mean baseline LDL-c 193.4 mg/dl	4-week dietary and placebo run-in phase, then randomized to: atorva 10 mg or simva 20 mg qd or to a higher dose atorva 20 or simva 40 mg qd for 6 weeks. Followed by 1-week washout period, then switched to alternate drug in corresponding dose for 6 weeks.	Efficacy analysis for 251 patients. **LDL-c reduction from baseline at 6 weeks:** atorva 10 mg: 36.7% ± 13.3 simva 20 mg: 34.8% ± 14 atorva 20 mg: 42.1% ± 15.6 simva 40 mg: 41% ± 15.9 (p>0.05 for atorva 10 mg vs. simva 20 mg, and atorva 20 mg vs. simva 40 mg) **HDL:** (p>0.05) Atorva 10 mg increased 8.1 % Atorva 20 mg increased 8.5% Simva 20 mg increased 8.7 % Simva 40 mg increased 9.3 % **Trigs:** (p>0.05) Atorva 10 mg reduction 22% Atorva 20 mg reduction 25% Simva 20 mg reduction 21.5% Simva 40 mg reduction 21.4%
Insull et al. 2001 R, OL, MC, not ITT 1,424 patients randomized (n= 730 atorva, 694 simva) First 6 weeks of planned 54 weeks Supported by grant from Parke-Davis.	Men or women 18-80 years with or without CHD and with or without Type 2 DM with elevated LDL. Mean baseline LDL-c Atorva 181.2 mg/dl Simva 181.9 mg/dl	8-week dietary run-in with NCEP step 1 or 2 diet. Eligible patients randomized to: atorva 10 mg qd or simva 10 mg qd.	Efficacy analysis for 1,378 patients. **LDL-c reduction from baseline at 6 weeks:** atorva 10 mg: 37.2% simva 10 mg: 29.6% (p<0.0001) **Reaching NCEP goal at 6 weeks:** atorva 10 mg: 55.6% simva 10 mg: 38.4% (p<0.0001) **HDL increased:** Atorva: 7.4% Simva: 6.9% (NS) **Trigs reduction:** Atorva: 27.6% Simva: 21.5% (p<0.0001)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Recto et al. 2000 R, OL, MC, crossover, not ITT 258 (?) patients (n= 125 atorva, 126 simva) 12 weeks Study supported by grant from Merck.	No differences in ADEs reported between groups. 1 patient in simva 20 mg group withdrawn due to ADE vs. 2 in atorva 10 mg and 3 in atorva 20 mg group. 2 serious ADEs in atorva 20 mg group. Myalgia occurred in 1 simva 20 mg vs. 2 atorva 10 mg patients. One patient in simva 40 mg group experienced elevation in ALT >3x ULN. <u>Dose equivalence</u> Atorva 10 mg qd ≈ simva 20 mg qd. Atorva 20 mg ≈ simva 40 mg qd.
Insull et al. 2001 R, OL, MC, not ITT 1,424 patients randomized (n= 730 atorva, 694 simva) First 6 weeks of planned 54 weeks Supported by grant from Parke-Davis.	No differences in treatment-related ADEs: atorva 5.8% vs. simva 2.9%. No reports of myopathy. 2 atorva patients had elevated ALT or AST >3x ULN. <u>Equivalent doses not compared.</u>

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Illingworth et al. 2001 R, DB, MC, not ITT 826 patients randomized (n= 408 atorva, 405 simva) 36 weeks 5 authors employed by Merck. Merck assisted in preparation of manuscript.	Men or women 21-70 years with elevated cholesterol. Mean baseline LDL-c Atorva 206 mg/dl Simva 209 mg/dl	4-week dietary run-in phase followed by randomization to 6 weeks of: atorva 20 mg or simva 40 mg qd, then 6 weeks of atorva 40 mg or simva 80 mg qd. If CK ≤ 5x ULN, patients were eligible for 24 weeks of atorva or simva 80 mg qd.	Efficacy analysis for 813 patients. **LDL-c reduction from baseline at 6 weeks:** atorva 20 mg= 46.1% vs. simva 40 mg= 42.4% **LDL-c reduction from baseline at 2nd 6 weeks:** atorva 40 mg= 51.3% vs. simva 80 mg= 48.8% **LDL-c reduction from baseline at 36 weeks:** atorva 80 mg= 53.6% vs. simva 80mg= 48.1% (p≤ 0.001 for all 3 comparisons) **HDL increased:** **Week 6:** atorva 20 mg= 7.3% vs. simva 40 mg= 8.5% (NS) **Week 12:** atorva 40 mg= 6.4% vs. simva 80 mg= 9.7% (p<0.001) **Week 18-36:** atorva 80 mg= 3% vs. simva 80 mg= 7.5% (p<0.001) **Trigs reduction:** atorva 20 mg= 23.6% vs. simva 40 mg= 22.4% atorva 40 mg= 31.6% vs. simva 80 mg= 25.9% atorva 80 mg= 31.3% vs. simva 80 mg= 23.6% (p≤ 0.05 for all 3 comparisons)
Branchi et al. 2001 R, OL, not ITT 200 patients randomized (n= 100 atorva, 100 simva) Up to 6 months Role and source of funding not reported.	Men or women with hypercholesterolemia not controlled with diet. Mean baseline LDL-c Atorva 228.2 mg/dl Simva 235.1 mg/dl	8-week dietary run-in, then randomization to: atorva 10 mg or simva 20 mg qd.	Efficacy analysis for 199 patients. **LDL-c reduction from baseline at 2 months:** **a**torva: 148.7 mg/dl (34.8%) simva: 158.4 mg/dl (32.6%)(NS) **HDL increase from baseline at 2 months (n=235, adjusted for baseline values):** **a**torva: 4.3% simva: 9.0% (p<0.05) **Trigs reduction from baseline at 2 months:** atorva: 27.4% simva: 24.8% (NS)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Illingworth et al. 2001 R, DB, MC, not ITT 826 patients randomized (n= 408 atorva, 405 simva) 36 weeks 5 authors employed by Merck. Merck assisted in preparation of manuscript.	HDL elevation was primary endpoint. ADEs similar during first 12 weeks of study. At end of 24-week period, 23.4% of atorva 80 mg vs. 11.9% of simva 80 mg experienced an ADE. (p<0.001). Difference due primarily to GI ADE (diarrhea). More in atorva 80 mg group (12.2%) vs. simva 80 mg group (3.9%) experienced laboratory ADEs (p<0.001). More discontinued treatment due to laboratory ADEs in atorva 80 mg (4.1%) vs. simva 80 mg group (0.8%) (p<0.001). Clinically significant elevations (>3x ULN) in ALT and AST observed significantly more often in atorva 80 mg vs. simva 80 mg group. ALT elevations especially prominent in women in atorva group. No myopathy reported in any group. A significantly higher number of women randomized to the atorva group.
Branchi et al. 2001 R, OL, not ITT 200 patients randomized (n= 100 atorva, 100 simva) Up to 6 months Role and source of funding not reported.	Significant number withdrew from treatment after 2 months. 46 required an increase in dose (20 atorva vs. 26 simva); 10 refused to continue; 8 stopped treatment during a recent illness. No differences in ADEs noted. 55 atorva vs. 58 simva patients completed 6 months of follow up. Responses similar to that seen at 2 months observed. HDL still significantly increased in the simva vs. atorva group. <u>Dose equivalence</u> Atorvastatin 10 mg qd ≈ simvastatin 20 mg qd

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Karalis et al. 2002 R, OL, MC, not ITT 1,732 patients randomized 6 weeks Pfizer supported and participated in the trial.	Men and women 18-80 years with LDL-c ≥190 mg/dl if no risk factors, or ≥160 mg/dl if 2 or more risk factors, or ≥130 mg/dl for those with CHD. Mean baseline LDL-c 178-182 mg/dl	4-week dietary run-in followed by randomization to: atorva 10 mg qd (n=650) or atorva 80 mg qd (n=216) or simva 20 mg qd (n=650) or simva 80 mg qd (n=216)	Efficacy analysis for 1694 patients. **LDL-c decrease from baseline at 6 weeks:** atorva 10 mg= 37% vs. simva 20 mg = 35% (p<0.025) atorva 80 mg= 53% vs. simva 80 mg= 47% (p<0.0001) **HDL increase from baseline:** atorva 10 mg= 5% vs. simva 20 mg= 6% atorva 80 mg= 2% vs. simva 80 mg= 6% (p<0.0001) **Trigs reduction from baseline:** atorva 10 mg= 18% vs. simva 20 mg= 14% (p<0.025) atorva 80 mg= 28% vs. simva 80 mg= 23% (p<0.025)
Kastelein et al, 2000 **R, DB, PC** 826 patients (n=406 atorva, 405 simva) 36 weeks Supported by a grant from Merck Research Laboratories	Men and women with LDL-c >160 mg/dL and triglycerides <350 mg/d Mean baseline LDL-c simva: 208.7 mg/dL atorva: 205.8 mg/dL	Atorva 20 mg qd for 6 weeks, then 40 mg qd or simva 40 mg qd for 6 weeks then 80 mg qd.	**Increase in HDL-c (average of results from weeks 6 and 12):** **s**imva 9.1% vs atorva 6.8% (p<0.001) simvastatin 80mg: 9.7% atorvastatin 40mg: 6.4% (p<0.001) simva 40mg vs atorva 20mg (NS, percent change not reported)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Karalis et al. 2002 R, OL, MC, not ITT 1,732 patients randomized 6 weeks Pfizer supported and participated in the trial.	Patients in atorva 80 mg vs. simva 80 mg group reported higher incidence of ADEs (46% vs. 39%) and discontinuation due to ADEs (8% vs. 5%) . Neither of these differences was statistically significant. <u>Dose equivalence</u> Atorva 10 mg>Simva 20 mg. Atorva 80 mg>Simva 80 mg.
Kastelein et al, 2000 **R, DB, PC** 826 patients (n=406 atorva, 405 simva) 36 weeks Supported by a grant from Merck Research Laboratories	No difference between the 2 drugs in tolerability profile after 12 weeks of treatment. <u>Dose equivalence</u> simva 80mg >atorva 40mg simva 40mg ≈ atorva 20mg

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Olsson et al. 2003 R(1:1), DB, MC, ITT 1087 patients randomized (n= 552 atorva, 535 simva) 52 weeks Supported by Pfizer.	White men and women 35-75 years with cardiovascular disease and LDL-c ≥ 155 mg/dl (4.0 mmol/L) Mean baseline LDL-c 5.19 mmol/L (calculated 200 mg/dl)	Dietary counseling during 4-week run-in phase. Patients on lipid-lowering therapy added 4-week washout period, then randomized to: atorvastatin 20 mg or simvastatin 20 mg, both titrated to 40 mg. Dose doubled at week 8 for patients not meeting NCEP target.	Efficacy analysis for 1087 patients. **LDL-c reduction at 8 (and 52) weeks:** atorva: 46%* (49%*) simva: 40% (44%) (*p<.001 vs. simva) **HDL increase at 8 (and 52) weeks:** atorva: -0.1%* (6.3%) simva: 3.3% (8.3%) (*p<.001 vs. simva) **Trigs reduction at 8 (and 52) weeks:** atorva: 23%* (24%*) simva: 14% (16%) (*p<.001 vs. simva) **Achieved NECP LDL-c goal at 8 (and 52) weeks:** atorva: 45%* (61%*) simva: 24% (41%) (*p<.001 vs. simva) 45% atorva vs. 24% simva patients remained at 20 mg

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Olsson et al. 2003 R(1:1), DB, MC, ITT 1087 patients randomized (n= 552 atorva, 535 simva) 52 weeks Supported by Pfizer.	ADE comparable between groups. 12 (2.2%) atorva and 13 (2.4%) simva patients had muscular symptoms (e.g., myalgia, myositis). 1 serious drug-related ADE in simva patient, with exacerbation of arm fascitis. Withdrawals due to ADE: 20/556 (3.6%) atorva vs. 14/537 (2.6%) simva. 6 withdrawals serious, with atorva heart failure, cerebral infarction and 2 malignancies; and simva acute MI and chest pain. No significant changes in either group for S-ALT, S-AST or CK. 1 patient in each group withdrawn due to elevated liver aminotransferase.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Kadikoylu et al, 2003 R, DB 61 patients randomized (n=35 atorva, 26 simva) 24 weeks Funding not reported	Men and women with at least 2 coronary risk factors and LDL-c levels >130 mg/dL. <u>Mean baseline LDL-c</u> atorva: 168.5 mg/dL simva: 172.1 mg/dL	Atorva 10 mg qd or simva 10 mg qd . When target level of LDL-c was not reached at 12 weeks according to ATP-III, dosage was increased to 20 mg qd.	**LDL-c goal reached at 24 weeks (all patients):** atorva: 85.7% simva: 84.6% (NS) **Diabetics only (n=23):** atorva: 64.3% simva: 55.6% (NS) **LDL-c reduction from baseline at 24 weeks:** atorva: 38.6% simva: 33.6% (NS) **HDL-c increase from baseline at 24 weeks:** atorva: 12.6% simva: -0.6% (NS) **Trigs change from baseline at 24 weeks:** atorva: -15.8% simva:+2.0% (NS)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Kadikoylu et al, 2003 R, DB 61 patients randomized (n=35 atorva, 26 simva) 24 weeks Funding not reported	Adverse effects seen in 5 patients (14.2%) atorva and 3 patients (11.5%) in simva group (headache, diarrhea, constipation, myalgia). Elevations in ALT>3 times the upper limit of normal and in CK >5 times the upper limit of normal did not occur. No discontinuations due to adverse effects; no significant differences between groups in adverse effects, adverse effects not dose-related. Equivalent doses not compared

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Ballantyne et al, 2003 R, DB, MC 917 patients randomized(n=464 atorva, 453 simva) 24 weeks Supported by a grant from Merck	Men and women 21-75 with LDL-c >130 mg/dL in CHD patients, >160 mg/dL in patients without CHD and with 2 or more risk factors, and >190 mg/dL in patients without CHD and with <2 risk factors; patients with diabetes were considered CHD equivalents; eligible LDL-c was >130 mg/dL in patients with HDL-c <40 mg/dL (men) and <50 mg/dL (women) plus 2 risk factors. All had triglyceride levels <400 mg/dL. Mean baseline LDL-c	Atorva 80 mg qd or simva 80 mg qd for 24 weeks.	**Increase in HDL-c from baseline, average of weeks 18 and 24** **Patients with baseline HDL-c <40mg/dL (n=267):** atorva: 2.1% simva: 5.4% (NS) **Patients with baseline HDL-c ≥40mg/dL (n=650):** atorva: 2.1% simva: 5.43% (NS) **Patients without metabolic syndrome (n=437):** atorva: 2.8% simva: 5.6% (NS)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Ballantyne et al, 2003 R, DB, MC 917 patients randomized(n=464 atorva, 453 simva) 24 weeks Supported by a grant from Merck	No difference between groups in number of drug-related clinical gastrointestinal adverse events. Most common GI adverse events were diarrhea (simva 1.3%; atorva 3.0%), constipation (simva 1.3%; atorva 1.5%), and nausea (simva 1.8%; atorva 0.9%). Most common drug-related muscular AEs resulting in discontinuation were myalgia, arthralgia, muscular weakness, muscular cramp, musculoskeletal stiffness, and body ache. Patients treated with atorva more likely to have elevations in ALT >3 times the upper limit of normal (difference -2.4%; 95% CI -4.3 to -0.7; p=0.007) Equivalent doses not compared

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Chan, et al, 2004 R, Blinded, SC 10 week dietary run-in; 18 weeks of treatment. 120 patients (n=60 simva; n=60 atorva) No industry support mentioned	Men and women 20-75 with Type 2 diabetes with mixed hyperlipidaemia (serum trig 203.7-398.6 mg/dL and LDL-c >=131.5 mg/dL) <u>Mean baseline LDL -c:</u> atorva: 171.3 mg/dL simva: 160.5 mg/dL	10 week NIH NCEP Step 1 dietary run-in and patients on lipid-lowering drugs did a 4 week wash-out before starting. atorva: 10 mg/d for 9 weeks then increased to 20 mg/d for 9 weeks simva: 20 mg/d for 9 weeks and then increased to 40 mg/d for 9 weeks.	**% patients reaching the LDL-c target (<100 mg/dL)** atorva: 74.1% simva: 75.4% **% patients reaching the TG target (151 mg/dL):** atorva: 27.8% simva: 35.1% **% patients reaching both targets:** atorva: 22.2% simva: 29.8% **LDL-c Change from baseline (approx. from table):** atorva 10 mg:-37% atorva 20mg:-28% simva 20mg:-42% simva 40 mg:-40% **HDL-c Change from baseline (approx. from table):** atorva 10 mg:+4% atorva 20mg:<=+1.0% simva 20mg:+4% simva 40 mg:+4.5% **Trig change from baseline (approx. from table):** atorva 10 mg:-20% atorva 20mg:-25% simva 20mg:-20% simva 40 mg:-25% *no p-values given*

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Chan, et al, 2004	No adverse events discussed in detail.
R, Blinded, SC 10 week dietary run-in; 18 weeks of treatment. 120 patients (n=60 simva; n=60 atorva) No industry support mentioned	Atorva: 5 patients withdrew (8.3%) Simva: 7 patients withdrew (11.7%) reason stated for both groups withdrawals: "mainly because of non compliance" Overall drug compliance was 91.5%. No subject developed a significant rise in liver enzymes or in CPK during study.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
	Atorvastatin vs. Multiple Statins		
Hunninghake et al. 1998 R, OL, MC, not ITT 344 patients randomized (n= 85 atorva, 82 fluva, 83 lova, 87 simva) 54 weeks Funded by Parke-Davis. One author employed by Parke-Davis.	Men or women 18-80 years at risk for CHD and elevated cholesterol. <u>Mean baseline LDL-c</u> Atorva 205 mg/dl Fluva 201 mg/dl Lova 206 mg/dl Simva 210 mg/dl	8-week optional dietary phase, 4-week dietary run-in followed by randomization to atorva 10 mg, fluva 20 mg, lova 20 mg or simva 10 mg qd. Doses titrated at 12-week intervals until LDL-c goal achieved or maximum dosage reached (atorva 80 mg, fluva 40 mg , lova 80 mg, simva 40 mg qd). If goal not reached with statin, colestipol added. Colestipol added = atorva 2%, fluva 67%, lova 24%, simva 24%.	Efficacy analysis for 337 patients (median dose/day). **LDL reduction from baseline at 54 weeks :** atorva 10 mg: 36% fluva 40 mg: 22%* lova 40 mg: 28%* simva 20 mg: 33% **HDL increase at 54 weeks:** atorva 9 % fluva 6 % lova 10% simva 11% **TRIGS reduction at 54 weeks:** atorva 20% fluva +2%* lova 16% simva 11% **Achieved LDL-c goal at 54 weeks:** atorva 95% vs. fluva 60%,* lova 77%,* simva 83%.* (*p<0.05 vs. atorva).

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Hunninghake et al. 1998 R, OL, MC, not ITT 344 patients randomized (n= 85 atorva, 82 fluva, 83 lova, 87 simva) 54 weeks Funded by Parke-Davis. One author employed by Parke-Davis.	ADEs similar across treatment groups prior to addition of colestipol to statin therapy at 24 weeks. At 54 weeks there were more ADEs in the fluva and lova groups than in the atorva or simva groups primarily GI in nature. Withdrawal for ADEs were 3% atorva, 4% fluva, 8% lova and 5% simva. One lova-treated patient experienced an elevation in ALT >3x ULN. Other clinically insignificant elevations in ALT or AST occurred in all groups. One patient receiving fluva experienced acute pancreatitis. No myopathy observed. No details on ADE and statin dose. Equivalent doses not compared; treat to target.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Brown et al. 1998 R, OL, MC, not ITT 318 patients randomized (n= 80 atorva, 80 fluva, 81 lova, 77 simva) 54 weeks Study funded by Parke-Davis. One author employed by Parke-Davis.	Men and women 18-80 years with documented CHD and LDL-c 130-250 mg/dl. Mean baseline LDL-c 173 mg/dl	Optional 8-week dietary phase, 4-week dietary run-in, then randomization to: atorva 10 mg, fluva 20 mg, lova 20 mg, or simva 10 mg qd. Doses could be titrated at 12-week intervals until LDL-c goal or maximum dose reached (atorva 80 mg, fluva 40 mg, lova 80 mg, or simva 40 mg qd). If goal not reached with statin, colestipol added (atorva 8%, fluva 76%, lova 15%, simva 33%).	Efficacy analysis for 308 patients (median dose/day). **LDL reduction from baseline at 54 weeks:** atorva 20 mg: 41% fluva 80 mg +colestipol 20 g: 30%* lova 80 mg: 41% simva 40 mg: 37% **HDL increase at 54 weeks:** atorva: 7% fluva: 7% lova: 12% simva: 11% **Trigs reduction at 54 weeks:** atorva: 19% vs. fluva: 2%,* lova: 14%, simva: 15% **Achieved LDL-c goal at 54 weeks:** atorva 83% vs. fluva 50%*, lova 81%, simva 75% (*p<0.05 vs. atorva)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Brown et al. 1998 R, OL, MC, not ITT 318 patients randomized (n= 80 atorva, 80 fluva, 81 lova, 77 simva) 54 weeks Study funded by Parke-Davis. One author employed by Parke-Davis.	ADEs similar across treatment groups at 54 weeks, except fluvastatin where patients also receiving colestipol experienced a 2 fold increase in GI ADEs. Withdrawal for ADEs similar among groups, included 3 atorva, 4 fluva, and 2 each for lova and simva. 1 lova patient experienced pancreatitis. Two fluva patients had elevations in either ALT or AST >3x ULN. No myopathy observed. No details on ADEs and statin dose. Equivalent doses not compared; treat to target.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Jones et al. 1998 **Jones et al. 2004** R, OL, MC, not ITT 534 patients randomized 8 weeks Study funded by Parke-Davis. Parke-Davis Research played role in some portion of the study.	Men or women 18-80 years with LDL ≥ 160 mg/dl. Mean baseline LDL-c Range 192-244 mg/dl	6-week dietary run-in phase, then randomization to one of 15 treatment groups: atorva 10, 20, 40, 80 mg fluva 20 or 40 mg lova 20, 40, or 80 mg prava 10, 20 or 40 mg simva 10, 20 or 40 mg qd.	Efficacy analysis for 522 patients. **LDL reduction from baseline at 8 weeks:** atorva 10 mg: 38% (n=73) / atorva 20 mg: 46% (n=51) atorva 40 mg: 51% (n=61) / atorva 80 mg: 54% (n=10) fluva 20 mg: 17% (n=12) / fluva 40 mg: 23% (n=12) lova 20 mg: 29% (n=16) / lova 40 mg: 31% (n=16) lova 80 mg: 48% (n=11) prava 10 mg: 19% (n=14) / prava 20 mg: 24% (n=41) prava 40 mg: 34% (n=25) simva 10 mg: 28% (n=70) / simva 20 mg: 35% (n=49) simva 40 mg: 41% (n=61) **HDL increase:** All similar (ranging from 3% ot 9%), except atorva 80 mg and fluva 40 mg, with reduction in HDL. Simva 40 mg increase significantly greater than atorva. **Trigs reduction:** All similar, except atorva 40 mg produced a greater reduction.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Jones et al. 1998 **Jones et al. 2004** R, OL, MC, not ITT 534 patients randomized 8 weeks Study funded by Parke-Davis. Parke-Davis Research played role in some portion of the study.	ADEs similar across treatment groups. 1 patient on atorva 20 mg developed myalgia judged unrelated to treatment. No clinically important elevations in liver transaminase or CK. <u>Dose equivalence</u> Atorvastatin 10 mg ≈ lovastatin 40 mg ≈ pravastatin 40 mg ≈ simvastatin 20 mg qd. Atorvastatin 20 mg ≈ lovastatin 80 mg ≈ simvastatin 40 mg qd.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Wolffenbuttel et al. 1998 R, OL, MC. cross-over, ITT 78 patients 4 weeks on each treatment Supported by Parke-Davis; one author employed by Parke-Davis.	Men and women 18-70 years with LDL-c 160-240 mg/dl. Mean baseline LDL-c 215 mg/dl	4-week dietary run-in then randomized to: atorva 5 mg or atorva 20 mg or simva 10 mg or prava 20 mg qd for 4 weeks. After washout, patients were switched to alternate treatment.	Efficacy analysis for 78 or 76 patients. **LDL-c reduction from baseline:** atorva 5 mg: 27% atorva 20 mg 44% (p<0.05 vs. simva and prava) prava 20 mg 24% simva 10 mg 28% **HDL increase from baseline:** atorva 5 mg 2% atorva 20 mg 8% prava 20 mg 3% simva 10 mg 1% (NS) **Trigs reduction from baseline:** atorva 5 mg 16% atorva 20 mg 23% (p<0.05 vs. simva and prava) prava 20 mg 11% simva 10 mg 8%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Wolffenbuttel et al. 1998 R, OL, MC. cross-over, ITT 78 patients 4 weeks on each treatment Supported by Parke-Davis; one author employed by Parke-Davis.	ADEs were similar between groups and no serious ADEs or withdrawal from groups as a result of ADEs were reported. <u>Dose equivalence</u> Atorvastatin 5 mg = pravastatin 20 mg = simvastatin 10 mg qd

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Gentile et al. 2000 R, OL, MC, not ITT 412 patients randomized 24 weeks Supported in part (60%) by MURST, Italy.	Men and women 50-65 years with type 2 diabetes mellitus and LDL-c >160 mg/dl Mean baseline LDL-c 199-218 mg/dl	6-week dietary run-in phase followed by randomization to: atorva 10 mg qd lova 20 mg qd prava 20 mg qd simva 10 mg qd or placebo for 24 weeks.	Efficacy analysis for 409 patients **LDL-c reduction from baseline:** atorva 37% (*p<0.05 vs. other statins) lova 21% prava 23% simva 26% placebo 1% **HDL increase from baseline:** atorva 7.4% lova 7.2% prava 3.2% (p<0.05 vs. other statins) simva 7.1% placebo 0.5% **Trigs reduction from baseline:** atorva 24% (p<0.05 vs. other statins) lova 11% prava 12% simva 14% placebo 1%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Gentile et al. 2000 R, OL, MC, not ITT 412 patients randomized 24 weeks Supported in part (60%) by MURST, Italy.	ADEs similar for all groups. Withdrawal for ADEs: 1 atorva, 1 lova and 1 prava patient. No clinically important elevation in ALT, AST or CK observed in any group. Equivalent doses not compared.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Andrews et al. 2001 R (4:1:1:1:1), OL, MC, not ITT 3,916 patients randomized 54 weeks Supported by grant from Pfizer. One Pfizer employee acknowledged for analysis and interpretation of data.	Men and women 18-80 years with elevated cholesterol, with or without CHD. <u>Mean baseline LDL-c</u> 176-179 mg/dl	Randomization to: Atorva 10 mg qd Fluva 20 mg qd Lova 20 mg qd Prava 20 mg qd or Simva 10 mg qd for 54 weeks. Doses were doubled until LDL-c goal or maximum doses were reached.	**Efficacy analysis for 3,757 patients (mean dose).** <u>LDL-c reduction from baseline at 54 weeks:</u> atorva (24 mg) 42% (p<0.01 vs. other statins) fluva (62 mg) 29% lova (52 mg) 36% prava (31 mg) 28% simva (23 mg) 36% <u>HDL increase from baseline at 54 weeks (NS):</u> atorva 5% fluva 6% lova 5% prava 6% simva 6% <u>Trigs reduction from baseline at 54 weeks:</u> atorva 19% (p<0.01 vs other statins) fluva 7% lova 12% prava 9% simva 13% <u>Achieved LDL-c goal at 54 weeks (p not reported):</u> atorva 76% fluva 37% lova 49% prava 34% simva 58%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Andrews et al. 2001 R (4:1:1:1:1), OL, MC, not ITT 3,916 patients randomized 54 weeks Supported by grant from Pfizer. One Pfizer employee acknowledged for analysis and interpretation of data.	ALT elevation >3x ULN occurred in 10 (0.5%) atorva patients vs. 1 patient each (0.2%) in fluva, prava and simva groups. None in lova. Withdrawal due to ADEs occurred in 7% atorva vs. 13% fluva vs. 8% lova vs. 4% prava vs. 8% simva patients. Myalgia occurred similarly in all groups. Serious treatment related ADEs occurred in 2 atorva patients (elevated CK , muscle cramps and rash) and 1 patient in simva (gastroenteritis). No details on dose for withdrawals or serious ADEs. Questionable why doses were not doubled for more patients to reach NCEP goals. Equivalent doses not compared.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Schaefer et al. 2004 R, OL, MC, ITT crossover design 196 patients studied: 99 patients randomized and 97 controls 36 weeks Supported by investigator-initiated research contracts from Parke-Davis/Pfeixer, and Otsuka America Pharmaceuticals, Inc.	Men and women with a mean age of 61.4 years with CHD and with LDL-c >130 mg/dl while off lipid-lowering drugs for 6 weeks. Mean baseline LDL-c : Not reported	4 week dietary run-in, then randomization to a dosing schedule that increased every 4 weeks (12 weeks total): fluva: 20 mg/d; 40 mg/d; 80 mg/d prava: 20 mg/d; 40 mg/d (8 weeks at this max dose) lova: 20 mg/d; 40 mg/d; 80 mg/d simva: 20 mg/d; 40 mg/d (8 weeks at this max dose) atorva: 20 mg/d; 40 mg/d; 80 mg/d for all 97 controls After the 12th week, an 8 week placebo period occurred. Then the patients were crossed over between atorv and another statin for 12 weeks (dosage increased every 4 weeks as before). 36 weeks total	*% change in lipoproteins data includes pre- and post-crossover data combined.* Mean % change in fasting lipoproteins after treatment (p-values are for paired comparisons between same doses of statins): **fluva 20/40/80 vs atorva 20/40/80:** LDL-c: -8%,-17%,-22% vs -34%,-45%,-51% (all have p<0.0001) HDL-c: +3%,+3%,+3% vs +2%,+6%,+1% (p not stated) trigs: -5%,-1%, 0% vs -20% (p<0.05), -25% (p<0.001), -33% (p<0.0001) **lova 20/40/80 vs atorva 20/40/80:** LDL-c: -20%,-28%,-31% vs -38%,-45%,-53% (all have p<0.0001) HDL-c: +4%,+3%,+9% vs +8% (p<0.01),+3% (p not stated),+1% (p not stated) trigs: -10%,-17%,-19% vs -27%,-32%,-32% (all have p<0.01) **prava 20/40/40 vs atorva 20/40/80:** LDL-c: -22%,-24%,-26% vs -39%,-46%,-50% (all have p<0.0001) HDL-c: +9%,+10%,+11% vs +8%,+5%,+6% (p not stated for any) trigs**:** -4%,-2%,-5% vs -9% (p not stated),-18% (p<0.05), -21% (p<0.05) **simva 20/40/40 vs atorva 20/40/80:** LDL-c: -28%,-39%,-39% vs -40% (p<0.001), -47% (p<0.01), -51%(p<0.001) HDL-c: +9%,+7%,+10% vs +5%,+5%,+4% (p not stated for any)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Schaefer et al. 2004 R, OL, MC, ITT crossover design 196 patients studied: 99 patients randomized and 97 controls 36 weeks Supported by investigator-initiated research contracts from Parke-Davis/Pfeixer, and Otsuka America Pharmaceuticals, Inc.	No safety data (adverse events and withdrawals) reported or discussed.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Fluvastatin vs. Lovastatin			
Nash 1996 R, OL, MC, ITT 137 patients randomized 8 weeks Funded by Sandoz Pharmaceuticals.	Men or women previously controlled on lovastatin 20 mg qd (LDL-c <150 mg/dl). After dietary washout phase, LDL-c required >160 mg/dl, trigs <350 mg/dl. <u>Mean baseline LDL-c</u> Not reported	6-week dietary/placebo washout period then randomization to: fluva 20 mg qd or lova 20 mg qd. After 4 weeks, fluva was increased to 40 mg qd.	Efficacy analysis for 137 patients. **LDL-c reduction from baseline at 8 weeks:** fluva: men and women 26% lova: men 29%, women 26% (NS) **HDL-c increase from baseline at 8 weeks (NS):** fluva: men: 7 %, women 8% lova: men 7%, women 4% **Trigs reduction from baseline at 8 weeks:** fluva: men 14%, women 10% lova: men 12%, women 20% **Achieved LDL-c goal (<160 mg/dl) at 4 weeks:** fluva: 85% lova: 91% (NS) **Achieved LDL-c goal (<160 mg/dl) at 8 weeks:** fluva: 89% lova: 91% (NS)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Fluvastatin vs. Lovas	
Nash 1996 R, OL, MC, ITT 137 patients randomized 8 weeks Funded by Sandoz Pharmaceuticals.	Myalgia occurred in 1 fluva vs. 2 lova patients. Musculoskeletal abnormalities existed significantly more often as a background medical condition in the lova group. 5 fluva and 1 lova patient experienced an increase in ALT or AST >3x ULN. No details on what dose of fluva patients experienced these ADEs.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Berger et al. 1996 R, OL, MC, ITT 270 patients randomized 6 weeks Sponsored by Merck and Co.	Age ≥20 years, 45% male, with serum triglyceride levels <400 mg/dl, not following cholesterol-reducing diet, and (a) LDL-c ≥190 mg/dl and ≤2 CHD risk factors, or (b) ≥160 mg/dl and ≥2 CHD risk factors, or (c) ≥130 mg/dl and definite CHD. Mean baseline LDL-c 187 mg/dl	5-week diet-only run-in phase, then randomization to: fluva 20 mg qd or lova 20 mg qd	Efficacy analysis for 270 patients. **LDL-c reduction from baseline:** fluva: 18% lova: 28% (p≤0.001) **HDL-c increase from baseline:** fluva and lova: ~8% (NS) **Trigs reduction from baseline:** fluva: 9% lova: 10% (NS) **Achieved NCEP LDL-c goal:** fluva: 24% lova: 37% (p=0.02)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Berger et al. 1996 R, OL, MC, ITT 270 patients randomized 6 weeks Sponsored by Merck and Co.	Withdrawals due to AEs: 8 fluva vs. 3 lova. Serious AEs (not considered drug related): 3 fluva vs. 5 lova. Total AEs: 54% fluva vs. 47% lova.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Davidson et al, 2003 R, DB, MC, PC, 838 patients randomized (n=337 fluva, 501 lova) 6 weeks 3 authors from Merck	Men and women >20 years with TG level < 4.5 mmol/L and one of the following LDL-c levels after 6-week run-in on NCEP Step I diet: (1) > 3.4 mmol/L with evidence of CHD or other atherosclerotic disease; (2) >4.1 mmol/L with >2 other CHD risk factors but no CHD or other atherosclerotic disease; (30 >4.9 mmol/L without CHD or other atherosclerotic disease and <2 other CHD risk factors. Mean baseline LDL-c fluva 20 mg: 181.7 mg/dL fluva 40 mg: 189.5 mg/dL lova 10 mg: 189.5 mg/dL lova 20 mg: 189.5	Fluva 20 or 40 mg qd or lova 10, 20, or 40 mg qd for 6 weeks.	**LDL-c reduction from baseline at 6 weeks:** fluva 20 mg: 18.8% fluva 40 mg: 22.6% lova 10 mg: 21.6% (p<0.05 vs fluva 20 mg) lova 20 mg: 27.3% (p<0.001 vs fluva 20 mg, p<0.05 vs fluva 40 mg) lova 40 mg: 31.8% (p <0.001 vs fluva 40 mg) **HDL-c increase from baseline at 6 weeks** (NS): fluva 20 mg: 3.5% fluva 40 mg: 4.3% lova 10 mg: 4.9% lova 20 mg: 5.7% lova 40 mg: 6.1% **Trigs reduction from baseline at 6 weeks** (NS): fluva 20 mg: 3.3% fluva 40 mg: 11.4% lova 10 mg: 6.4% lova 20 mg: 5.7% lova 40 mg: 11.3%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Davidson et al, 2003 R, DB, MC, PC, 838 patients randomized (n=337 fluva, 501 lova) 6 weeks 3 authors from Merck	No significant differences between treatments in any AE reported. Most common were GI disturbances, flatulence in 16 (3.2%) lova and 19 (5.6%) fluva patients 21 (4.2%) lova and 22 (6.5%) fluva patients withdrew due to adverse effects. 4 lova and 4 fluva patients reported serious adverse effects; only one (fecal occult blood/gastric ulcer in 1 patient treated with fluva 20mg considered treatment related. <u>Dose equivalence</u> lova 20 mg > fluva 40 mg

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
	Fluvastatin vs. Pravastatin		
Jacotot et al. 1995 R, DB, MC, both ITT and on treatment analysis 134 patients randomized 16 weeks Funding and participation by Sandoz Pharmaceuticals.	Men and women 18-75 years with LDL≥160 mg/dl and trigs ≤400 mg/dl Mean baseline LDL-c Fluva 216.4 mg/dl Prava 226.9 mg/dl	6-week dietary/placebo run-in phase then, randomization to: fluva 40 mg qd or prava 20 mg qd for 4 weeks. Doses doubled at 4 weeks and study continued another 12 weeks.	Efficacy analysis for 134 patients. **LDL-c reduction from baseline at 16 weeks:** fluva 40 mg bid: 29.6% prava 40 mg qd: 26.1% (NS) **HDL-c increase from baseline at 16 weeks:** fluva 40 mg bid: 7.5% prava 40 mg qd: 9% (p<0.001) **Trigs reduction from baseline at 16 weeks:** fluva 40 mg bid: 14.9% prava 40 mg qd: 2.8% (p<0.001)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Jacotot et al. 1995 R, DB, MC, both ITT and on treatment analysis 134 patients randomized 16 weeks Funding and participation by Sandoz Pharmaceuticals.	6 patients withdrew from study due to ADEs (3 in each group). No patient withdrew due to myopathic complaints or liver ADEs. More GI ADEs in fluva group. No patient experienced clinically significant elevation in ALT, AST or CK. <u>Dose equivalence</u> Fluvastatin 40 mg ≈ pravastatin 20 mg qd. Fluvastatin 40 mg bid ≈ pravastatin 40 mg qd.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
	Fluvastatin vs. Simvastatin		
Ose et al. 1995 R, DB, MC, ITT 432 patients randomized 6 weeks Funded by Merck.	Men and women 70 years of age or less and a total cholesterol ≥250 mg/dl. Mean baseline LDL-c 213-232 mg/dl w/o CHD 247-267 mg/dl with CHD	4-week dietary/placebo run-in, then randomized to: fluva 20 or 40 mg qd, or simva 5 or 10 mg qd for 6 weeks.	Efficacy analysis for 432 patients. **LDL-c reduction from baseline at 6 weeks:** fluva 20 mg: 21.8% fluva 40 mg: 25.9% simva 5 mg: 25.7% (p<0.01 vs fluva 20 mg) simva 10 mg: 29.9% (p<0.01 vs fluva 20 mg, p<0.05 vs fluva 40 mg) **HDL-c increase from baseline at 6 weeks:** fluva 20 mg: 6.3% fluva 40 mg: 13% simva 5 mg: 10.1% simva 10 mg: 12.2% (p<0.01 vs fluva 20 mg) **Trigs reduction from baseline at 6 weeks:** fluva 20 mg: 10% fluva 40 mg: 12.8% simva 5 mg: 11.5% simva 10 mg: 14.5% **Achieved NCEP LDL-c goal:** fluva 20 mg: 12% fluva 40 mg: 21% simva 5 mg: 24% (p<0.05 vs fluva 20 mg) simva 10 mg: 25% (p<0.01 vs fluva 20 mg)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Ose et al. 1995 R, DB, MC, ITT 432 patients randomized 6 weeks Funded by Merck.	Number of patients reporting ADEs similar across all groups. GI ADEs were more frequent in fluva vs. simva groups, especially at 40 mg qd dose. One fluva patient had ALT >3x ULN. <u>Dose equivalence</u> Fluvastatin 40 mg qd = simvastatin 5 mg qd for reducing LDL-c. Fluvastatin 40 mg qd = simvastatin 10 mg qd for NCEP goal reached.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Schulte et al. 1996 R, DB 120 patients randomized 10 weeks Funded by Astra.	Men and women 26-74 years with LDL-c >185 mg/dl and trigs <300 mg/dl. <u>Median baseline LDL-c</u> Fluva 218.5 mg/dl Simva 211.5 mg/dl	4-week dietary run-in phase and randomized to: fluva 40 mg qd or simva 20 mg qd for 4 weeks. After 4 weeks, dose was doubled and continued for 6 more weeks.	Unclear if all patients included in efficacy analysis: **LDL-c reduction from baseline at 4 and 10 weeks:** fluva 40 mg: 23.8% simva 20: 23.6% fluva 80 mg: 30.6% simva 40 mg: 34.4% (NS at 4 or 10 weeks) **HDL-c increase from baseline at 4 and 10 weeks:** fluva 40 mg: 7.1% simva 20 mg: 8% fluva 80 mg: 13.1% simva 40 mg: 12.3% (NS at 4 or 10 weeks) **Trigs reduction from baseline at 4 and 10 weeks:** fluva 40 mg: 2.1% simva 20 mg: +1% fluva 80 mg: 1.2% simva 40 mg: 2.3% (NS at 4 or 10 weeks)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Schulte et al. 1996 R, DB 120 patients randomized 10 weeks Funded by Astra.	Clinically insignificant differences in ADE. One patient in each group had elevations in AST or ALT >3x ULN. No clinically significant increase in CK was observed. <u>Dose equivalence</u> Fluvastatin 40 mg qd = simvastatin 20 mg qd. Fluvastatin 80 mg qd = simvastatin 40 mg qd.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Sigurdsson et al. 1998 R, DB, MC, not ITT 113 patients randomized 16 weeks Funded by grant from Merck. One author employed by Merck. Merck also supplied lovastatin and placebo.	Men or women with CHD. Mean baseline LDL-c 185-187 mg/dl	8-week dietary and 2 week-placebo run-in phase, then randomized to: fluva 20 mg qd or simva 20 mg qd for 16 weeks. Doses could be doubled at week 10 if TC >200 mg/dl at week 6.	Efficacy analysis for 110 patients. **LDL-c reduction from baseline at 16 weeks:** fluva: 25.3% simva: 39.9% (p<0.001) **HDL-c increase from baseline at 16 weeks:** fluva: 8.8% simva: 11.1% (NS) **Trigs reduction from baseline at 16 weeks:** fluva: 23.1% simva: 22.5% (NS) **Achieved LDL-c <200 mg/dl:** 49.1% fluva vs. 87.3% simva (p<0.001) 63% fluva patients vs. 18% simva patients increased dose to 40 mg qd (p<0.001)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Sigurdsson et al. 1998 R, DB, MC, not ITT 113 patients randomized 16 weeks Funded by grant from Merck. One author employed by Merck. Merck also supplied lovastatin and placebo.	ADEs similar between groups, with a trend to more GI ADEs in the fluva vs. simva group (8 vs. 4). The difference was not significant. No clinically important elevations in ALT, AST, or CK. Nonequivalent doses compared, treat to target.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
	Lovastatin Extended Release vs. Lovastatin Immediate Release		
Lukacsko et al, 2004 179 patients randomized (n= 90 lova ER, 89 lova IR) 12 weeks; crossover Funded by Andrx Laboratories, and all authors employed by same.	Men and women ages 21 to 70 with a TG level less than 350 mg/dL and plasma LDL-c within the following parameters: >100 mg/dl for patients with a history of CHD, peripheral vascular disease (PVD), or cerebrovascular disease (CVD); 130 mg/dl or higher for patients without a history of CHD, PVD, or CVD, but with 2 or more risk factors for heart disease; or 160 mg.dl or higher for patients without a history of CHD, PVD, or CVD, but with less than 2 risk factors for heart disease.	Lovastatin 20mg ER once daily vs lovastatin 20 mg IR once daily	Efficacy analysis for 179 patients. **LDL-c reduction from baseline at week 12 (from baseline to endpoint for treatment periods 2 and 4 combined, results for separate treatment periods not reported):** Lova ER: 26.4% Lova IR: 23.1% (difference -3.3%; p=0.0028; 95% CI -5.43% to -1.15%) **HDL-c increase from baseline to endpoint for treatment periods 2 and 4 combined (12 week treatment periods, results for separate treatment periods not reported):** Lova ER: 4.1% Lova IR: 4.3% (difference -0.2%; p=0.8584)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Lukacsko et al, 2004 179 patients randomized (n= 90 lova ER, 89 lova IR) 12 weeks; crossover Funded by Andrx Laboratories, and all authors employed by same.	No apparent trends by treatment in the incidence of treatment emergent signs and symptoms. Serious adverse events reported by 5 patients receiving ER lova (6 events: cholecystitis, accidental injury, cerebral ischemia, angina pectoris, enlarged uterine fibroids, and back pain), and 2 patients receiving IR lova (increased knee pain due to degenerative joint disease, and MI). Dose equivalence: lova ER > lova IR

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
	Lovastatin vs. Pravastatin		
McPherson et al. 1992 R, DB, MC, not ITT 217 patients randomized 8 weeks Merck funded the study.	Men and women 18-75 years with LDL-c ≥190 mg/dl with no risk factors or ≥ 160 mg/dl in those with 2+ risk factors. Mean baseline LDL-c 209-211 mg/dl	6-week dietary/placebo and washout phase followed by randomization to: lova 20 mg qd (n=73) or prava 10 mg qd (n=74) or prava 20 mg qd (n=70)	Efficacy analysis for 201 patients. **LDL-c reduction from baseline at 8 weeks:** lova 20 mg: 28% prava 10 mg: 24.5% prava 20 mg: 28.4% (all NS) **HDL-c increase from baseline at 8 weeks (p not reported):** lova 20 mg: 8.7% prava 10 mg: 10.8% prava 20 mg: 5.4% **Trigs reduction from baseline at 8 weeks:** lova 20 mg: 6.8% prava 10 mg: 0.9% prava 20 mg: 4.9% **High risk meeting NCEP goal:** lova: 29%, prava 10 mg: 25%, prava 20 mg: 26% (NS) **Moderate risk meeting NCEP goal:** lova 74%, prava 10 mg: 53%, prava 20 mg: 68% (NS)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
McPherson et al. 1992 R, DB, MC, not ITT 217 patients randomized 8 weeks Merck funded the study.	Adverse effects not different between groups. Difference in LDL-c lowering greater at 4 weeks in lova vs. prava 10 mg groups, however was not different at 8 weeks. LDL-c lowering in lova vs. prava 20 mg groups not different at any time. <u>Dose equivalence</u> lova 20 mg = prava 20 mg ≈ prava 10 mg.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
The Lovastatin Pravastatin Study Group 1993 R, DB, MC, not ITT 672 patients randomized 18 weeks Merck supported and participated in trial.	Men and women 25-75 years with hypercholesterolemia <u>Mean baseline LDL-c</u> 194-196 mg/dl	7-week dietary/placebo run-in phase followed by randomization to: lova 20 mg qd (n=339) or prava 10 mg qd (n=333) for 6 weeks. Then doses doubled to lova 40 mg qd or prava 20 mg qd for 6 weeks, then doubled to lova 80 mg (40 mg bid) qd or prava 40 mg qd for the remaining 6 weeks.	Unclear number of patients in efficacy analysis. 91% of patients completed trial. **LDL-c reduction from baseline at 6, 12 and 18 weeks:** lova 20 mg: 28% vs. prava 10 mg: 19% lova 40 mg: 33% vs. prava 20 mg: 25% lova 80 mg: 39% vs. prava 40 mg: 27% (p<0.01 all comparisons) **HDL-c increase from baseline at 18 weeks:** lova 80 mg: 19% prava 40 mg: 16% (NS) **Trigs reduction from baseline at 18 weeks:** lova 80 mg: 22% prava 10 mg: 15% (p<0.05)
Weir et al. 1996 R, DB, MC, not ITT 426 patients randomized 12 weeks Merck participated in study.	Men and women 20-65 years with hypercholesterolemia <u>Mean baseline LDL-c</u> Lova 195 mg/dl Prava 202 mg/dl	6-week dietary/placebo run-in followed by randomization to: lova 40 mg qd (n=211) or prava 40 mg qd (n=215).	Efficacy analysis for 423 patients. **LDL-c reduction from baseline at 12 weeks:** lova: 27.9% prava: 23.6% (NS) **HDL-c increase from baseline at 12 weeks:** lova: 8.5% prava: 8.2% (NS) **Trigs reduction from baseline at 12 weeks:** lova: 6% prava: 8.6% (NS) **Achieved NECP LDL-c goal:** lova 45% vs. prava 26% (p<0.001)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
The Lovastatin Pravastatin Study Group 1993 R, DB, MC, not ITT 672 patients randomized 18 weeks Merck supported and participated in trial.	No differences between groups for ADEs. No cases of myopathy reported. Liver transaminase levels >3x ULN occurred in one lova vs. 2 prava patients. <u>Equivalent doses not compared.</u>
Weir et al. 1996 R, DB, MC, not ITT 426 patients randomized 12 weeks Merck participated in study.	Primary endpoint was quality of life. No difference in quality of life between groups. No significant differences in ADEs or laboratory ADEs between groups. <u>Dose equivalence</u> Lova 40 mg = prava 40 mg qd.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Strauss et al. 1999 R, SB, Crossover, not ITT 31 patients randomized 12 weeks Merck and Bristol Myers Squibb provided active drug only.	Men and women with hypercholesterolemia <u>Mean baseline LDL-c</u> 185 mg/dl	4-week dietary run-in followed by randomization to: lova 10 mg qd or prava 10 mg qd for 4 weeks. Then a 4 week washout period followed by crossover to alternate statin for 4 weeks.	Efficacy analysis for 30 patients. **LDL-c reduction from baseline at 4 weeks:** lova: 24% prava: 19% (NS) **HDL-c increase from baseline at 4 weeks:** lova: 0.9% prava: 1.6% (NS) **Trigs reduction from baseline at 4 weeks:** lova: 15.3% prava: 19.4% (NS)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Strauss et al. 1999 R, SB, Crossover, not ITT 31 patients randomized 12 weeks Merck and Bristol Myers Squibb provided active drug only.	There were no differences in ADEs between groups. No cases of myopathy or clinical significant elevation in ALT or AST observed. <u>Dose equivalence</u> Lova 10 mg = prava 10 mg qd.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
	Lovastatin vs. Simvastatin		
Farmer et al. 1992 R, DB, MC, not ITT 544 patients randomized 24 weeks 3 primary authors employed by Merck.	Men and women 30-85 years with hypercholesterolemia <u>Mean baseline LDL-c</u> 191.4-193.4 mg/dl	6-week baseline dietary-placebo phase followed by randomization to: lova 20 mg qd (n=137) or lova 40 mg qd (n=134) or simva 10 mg qd (n=134) or simva 20 mg qd (n=135) for 24 weeks.	Efficacy analysis for 540 patients. **LDL-c reduction from baseline at 24 weeks:** lova 20 mg: 25.4% lova 40 mg: 31.2% simva 10 mg: 27.5% (NS) simva 20 mg: 34.7% (p<0.05) **HDL-c increase from baseline at 24 weeks:** lova 20 mg: 4.2% lova 40 mg: 7.4% simva 10 mg: 4.6% (NS) simva 20 mg: 4.6 (NS) **Trigs reduction from baseline at 24 weeks:** lova 20 mg: 10.5% lova 40 mg: 10.3% simva 10 mg: 3.9% (no significance reported) simva 20 mg: 10.3% (NS) **Achieved NCEP LDL-c goal (p not reported):** lova 20 mg: 33% lova 40 mg: 51% simva 10 mg: 41% simva 20 mg: 61%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Farmer et al. 1992 R, DB, MC, not ITT 544 patients randomized 24 weeks 3 primary authors employed by Merck.	No difference in ADEs between groups. Withdrawal for clinical or laboratory ADEs not different between groups. 1 patient in lova 40 mg group had ALT 3x ULN. <u>Dose equivalence</u> lova 20 mg = simva 10 mg qd lova 40 mg < or ≈ simva 20 mg qd.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Frohlich et al. 1993 R, DB, MC, not ITT 298 patients randomized 18 weeks Merck funded the study. Authors thanked Merck for coordination of data and their biostatistics groups.	Men and women 18-70 years with total cholesterol of 240-300 mg/dl (stratum 1) or >300 mg/dl (stratum 2) Mean baseline LDL-c Stratum 1: 200 mg/dl Stratum 2: 282-291 mg/dl	6-week dietary, 4 week-dietary-placebo run-in phase, then randomized to: lova 20 mg (n=149) or simva 10 mg (n=146). Doses doubled at 6 and 12 weeks if TC ≥200 mg/dl	Efficacy analysis for 296 patients. **LDL-c reduction from baseline at 18 weeks:** Stratum 1 (mean dose): lova 50 mg qd: 34.3% simva 26.4 mg qd 34.6% (NS) Stratum 2 (mean dose): lova 71.7 mg qd: 37.2% simva 36.9 mg qd.: 37.1% (NS) **HDL-c increase from baseline at 18 weeks:** Stratum 1 (mean dose): lova 50 mg qd: 2.7% simva 26.4 mg qd 7.0% (NS) Stratum 2 (mean dose): lova 71.7 mg qd: 8.8% simva 36.9 mg qd: 5.3% (NS)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Frohlich et al. 1993 R, DB, MC, not ITT 298 patients randomized 18 weeks Merck funded the study. Authors thanked Merck for coordination of data and their biostatistics groups.	Patients in Stratum 2 experienced more laboratory ADEs in lova group vs. simva group (8.3% vs 0% , p<0.05). There were said to be minor and well within normal ranges. No other safety differences between groups. 1 major laboratory ADE occurred in lova group in Stratum 2, thought not to be drug-related. <u>Dose equivalence</u> lova 20 mg = simva 10 mg lova 80 mg = simva 40 mg qd

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Pravastatin vs. Simvastatin			
Malini et al. 1991 R, OL, ITT 100 patients randomized 6 weeks Industry support not reported.	Men and women 18-70 years with total cholesterol ≥240 mg/dl Mean baseline LDL-c Prava 205 mg/dl Simva 209 mg/dl	4-week dietary-placebo run in phase then randomized to: prava 10 mg qd (n=50) or simva 10 mg qd (n=50)	Efficacy analysis for 100 patients. **LDL-c reduction from baseline at 6 weeks:** prava: 21.8% simva 10 mg: 33.1% (p<0.01) **HDL-c increase from baseline at 6 weeks:** prava: 7% simva: 10% (p<0.05) **Trigs reduction from baseline at 6 weeks:** prava: 5.8% simva: 12.3% (p<0.01)
Lefebvre et al. 1992 R, DB, MC, not ITT 291 patients randomized 6 weeks Study supported by Merck.	Men and women 18-79 years with total cholesterol ≥240 mg/dl Mean baseline LDL-c Prava 219 mg/dl Simva 223 mg/dl	4-week dietary-placebo run-in phase, then randomized to: prava 10 mg qd (n=141) or simva 10 mg qd (n=142)	Efficacy analysis for 283 patients. **LDL-c reduction from baseline at 6 weeks:** prava: 22% simva:32% (p<0.01) **HDL-c increase from baseline at 6 weeks:** prava: 5% simva: 7% (p=0.06) **Trigs reduction from baseline at 6 weeks:** prava: 6% simva: 13% (p<0.05)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Pravastatin vs. Simva	
Malini et al. 1991 R, OL, ITT 100 patients randomized 6 weeks Industry support not reported.	ADEs were reported in 4 prava patients vs. 2 simva patients. No patient withdrew from the study due to ADEs. <u>Dose equivalence</u> Equivalent doses not compared.
Lefebvre et al. 1992 R, DB, MC, not ITT 291 patients randomized 6 weeks Study supported by Merck.	ADEs similar between groups. No patient experienced a clinically significant increase in liver transaminases or CK. Authors report 9 laboratory ADEs in simva vs. 2 in prava groups. Details not provided for all incidents. <u>Equivalent doses not compared.</u>

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Lintott et al. 1993 R, DB, MC, not ITT 48 patients randomized 24 weeks Study supported by Merck.	Men or women with hypercholesterolemia Mean baseline LDL-c Prava 243 mg/dl Simva 250 mg/dl	6-week dietary-placebo phase then, randomization to: prava 10 mg qd (n=24) or simva 10 mg qd (n=24) for 6 weeks. At 12 and 18 weeks, doses doubled if LDL-c was >130 mg/dl to a maximum of 40 mg qd. At week 18, all patients switched to simva at 18-week dose.	Efficacy analysis for 47 patients. **LDL-c reduction from baseline at 6 weeks:** prava: 17% simva: 29% (no p-value provided) **LDL-c reduction from baseline at 18 weeks:** prava: 27% simva: 38% (p=0.001) **HDL-c increase from baseline at 18 weeks:** prava: 7% simva: 11% (NS) **Trigs reduction from baseline at 18 weeks:** prava: unchanged at 18 weeks simva: 11.8% 18/24 simva vs. 22/23 prava users titrated to maximum
Lambrecht et al. 1993 R, DB, MC, not ITT 210 patients randomized 6 weeks Industry support not reported.	Men or women 18-70 years with total cholesterol ≥250 mg/dl Mean baseline LDL-c Prava 214 mg/dl Simva 219 mg/dl	4-week dietary-placebo run-in phase, then randomized to: prava 20 mg qd (n=105) or simva 20 mg qd (n=105) for 6 weeks.	Efficacy analysis for 200 patients. **LDL-c reduction from baseline at 6 weeks:** prava: 29% simva: 38% (p<0.01) **HDL-c increase from baseline at 6 weeks:** prava: 7.3% simva: 6.7% (NS) **Trigs reduction from baseline at 6 weeks:** prava: 10.9% simva: 14.3% (NS) **Achieved LDL-c <160 mg/dl:** 78% simva vs. 64% prava (p=0.06) **Achieved LDL-c <130 mg/dl:** 46% simva vs. 19% prava (p<0.01)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Lintott et al. 1993 R, DB, MC, not ITT 48 patients randomized 24 weeks Study supported by Merck.	One simva patient experienced significant elevation in CK after beginning rigorous exercise program the day before. Simva was stopped and restarted with no further incident. One prava patient developed a rash and was withdrawn. Titrate to target, nonequivalent doses compared.
Lambrecht et al. 1993 R, DB, MC, not ITT 210 patients randomized 6 weeks Industry support not reported.	ADEs similar between groups. 3 ADEs reported >1%: myalgia (1.9%) and dyspepsia (1.9%) in simva group, and flatulence (1.9%) in prava group. 3 patients withdrawn due to ADEs: 1 in simva (malaise) and 2 in prava (malaise, nausea and palpitations; and flatulence) group. None of the events was considered serious. No clinically important changes in liver transaminases or CK. Nonequivalent doses compared.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Sweany et al., 1993 R, DB, MC, not ITT 550 patients 18 weeks Merck funded and participated in study.	Men and women 18-71 years with LDL-c ≥160 mg/dl Mean baseline LDL-c Prava 212 mg/dl Simva 207 mg/dl	6-week dietary/placebo run-in phase, then randomized to: prava 10 mg qd (n=275) or simva 10 mg qd (n=275) for 6 weeks. Doses doubled if LDL-c at weeks 6 and 12 were >130 mg/dl, up to a maximum of 40 mg qd for each statin.	Efficacy analysis number of patients not reported. **LDL-c reduction from baseline at 6 weeks:** prava: 19% simva: 30% (p<0.01) **LDL-c reduction from baseline at 18 weeks:** (mean dose) prava 32 mg/d: 26% simva 27 mg/d: 38% (p<0.01) **HDL-c increase from baseline at 18 weeks:** prava 12% simva 15% (p<0.05) **Trigs reduction from baseline at 18 weeks:** prava 14% simva 18% (p<0.05) **Achieved LDL-c <130 mg/dl** 65% simva vs. 39% prava

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Sweany et al., 1993 R, DB, MC, not ITT 550 patients 18 weeks Merck funded and participated in study.	5 patients in each group withdrew due to ADEs. Reasons in prava group: headache and tinnitus, rash, abdominal pain, GI complaints and dizziness. Reasons in simva group: GI in 3 patients, headache, and diarrhea and sinus tachycardia. Myalgia reported by 1 simva and 3 prava users. 1 prava patient stopped due to myalgia and muscle cramps with CK 3-10x ULN. CK elevation in other myalgia reports not clinically significant. 2 simva patients had CK elevation > 10x ULN, attributed to exercise (simva continued without further problems). No clinically significant elevations in AST or ALT. Nonequivalent doses compared. Treat to target.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Douste-Blazy et al. 1993 R, DB, MC, not ITT 273 patients randomized 6 weeks Study supported by Merck.	Men and women 22-75 years with an LDL-c ≥160 mg/dl Mean baseline LDL-c Prava 222 mg/dl Simva 224 mg/dl	4-week placebo/dietary run-in phase followed by randomization to: prava 20 mg qd (n=136) or simva 10 mg qd (n=137) for 6 weeks.	Efficacy analysis for 268 patients. **LDL-c reduction from baseline at 6 weeks:** prava: 25% simva: 28.3% (p<0.01) **HDL-c increase from baseline at 6 weeks:** prava: 6.1% simva: 6.3% (NS) **Trigs reduction from baseline at 6 weeks:** prava: 12.9% simva: 13.8% (NS) **Achieved LDL-c <130 mg/dl:** 16% prava vs. 22% simva **Achieved LDL-c <160 mg/dl:** 53% prava vs. 60% simva
Stalenhoef et al. 1993 R, DB, MC, not ITT 48 patients randomized 18 weeks Industry involvement not reported.	Men and women with primary hypercholesterolemia LDL-c >180 mg/dl Mean baseline LDL-c 316 mg/dl	6-week dietary/placebo run-in period followed by randomization to: prava 10 mg qd (n=24) or simva 10 mg qd (n=24) for 6 weeks. Doses doubled at 12 and 18 weeks to a maximum 40 mg qd.	Efficacy analysis for 46 patients. **LDL-c reduction from baseline at 18 weeks:** prava 40 mg: 33% (mean doses) simva 40 mg: 43% (p<0.01) **HDL-c increase from baseline at 18 weeks:** prava: 6% simva: 8% (NS) **Trigs reduction from baseline at 18 weeks:** prava: 13% simva: 15% (NS)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Douste-Blazy et al. 1993 R, DB, MC, not ITT 273 patients randomized 6 weeks Study supported by Merck.	Reported ADEs were similar between groups. Two patients in each group stopped the statin due to ADEs and were not serious. No patient withdrew due to a laboratory ADE. <u>Dose equivalence</u> prava 20 mg ≈ or < simva 10 mg qd.
Stalenhoef et al. 1993 R, DB, MC, not ITT 48 patients randomized 18 weeks Industry involvement not reported.	Two patients withdrew due to ADEs. No details provided. No clinically significant increases in ALT/AST or CK. <u>Nonequivalent doses compared.</u>

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Steinhagen-Thiessen 1994 R, DB, MC, not ITT 281 patients randomized 12 weeks Study supported by Merck.	Men or women 21-71 years with total cholesterol 220-280 mg/dl. Mean baseline LDL-c 174-176 mg/dl	4-week dietary/placebo run-in period followed by randomization to: prava 10 mg qd (n=138) or simva 5 mg qd (n=143) for 6 weeks. At 6 weeks, simva increased to 10 mg qd.	Efficacy analysis for 273 patients. **LDL-c reduction from baseline at 6 weeks:** prava 10 mg: 17.7% simva 5 mg: 23.3% (p<0.01) **LDL-c reduction from baseline at 12 weeks:** prava 10 mg: 16.5% simva 10 mg: 26.8% (p<0.01) **HDL-c increase from baseline at 12 weeks:** prava 10 mg: 8.3% simva 10 mg: 8.1% (NS) **Trigs reduction from baseline at 12 weeks:** prava 10 mg: 4.2% simva 10 mg: 9.5% (NS) **Achieved LDL-c <130 mg/dl:** prava 10 mg: 32-33% vs. simva 5 mg: 45% vs. simva 10 mg 59%
Sasaki et al. 1997 R, OL, C, not ITT 74 patients randomized 16 weeks Funding not reported.	Men or women with total cholesterol ≥220 mg/dl. Mean baseline LDL-c 177.7 mg/dl	Observation period (duration not stated), then randomization to: prava 10 mg qd or simva 5 mg qd for 8 weeks - then switched to alternate statin for another 8 weeks.	Efficacy analysis for 72 patients. **LDL-c reduction from baseline at 8 weeks:** prava: 23.1% simva: 31.1% (p<0.05) **HDL-c increase from baseline at 8 weeks:** prava: 6.6% simva: 7.9% (NS) **Trigs reduction from baseline at 8 weeks:** prava: 5.8% simva: 13% (NS) **Achieved LDL-c goal:**

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Steinhagen-Thiessen 1994 R, DB, MC, not ITT 281 patients randomized 12 weeks Study supported by Merck.	Most common treatment-related ADE was musculoskeletal complaints in simva group vs. digestive disturbances in prava group. 3 patients withdrew due to ADEs: 1 rash and 1 hepatitis (patient later found to be Hep B positive) in simva group, both judged unrelated to treatment. No details on 3rd withdrawal. 1 prava patient with CK elevation >10x ULN. No further details provided. <u>Dose equivalence</u> Simvastatin 5 and 10 mg > prava 10 mg qd
Sasaki et al. 1997 R, OL, C, not ITT 74 patients randomized 16 weeks Funding not reported.	No differences between groups. No clinically important laboratory changes. <u>Dose equivalence</u> Simvastatin 5 and 10 mg > prava 10 mg qd

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
	Rosuvastatin vs Atorvastatin		
Berne et al, 2005 **URANUS** R, DB, MC, not ITT 469 patients randomized 16 weeks Supported by AstraZeneca	Men or women with a history of type 2 diabetes for at least 3 months, being treated with diet, oral antidiabetic medication, insulin, or a combination of these treatments, and fasting LDL-C of >=3.3 mmol/L and triglycerides <6.0 mmol/L at enrollment.	6-week dietary run-in, then randomization to: rosuva 10 mg or atorva 10 mg for 4 weeks, then 12-week period of dose titration if patient had not reached European guideline goal (LDL-c <117 mg/dL): rosuva 20 mg or atorva 20 mg for 4 weeks. Further dose titrations up to to rosuva 40 mg or atorva 40 mg or 80 mg were performed at weeks 8 and 12 if patients were still not at goal.	Efficacy analysis for 441 patients (least squares mean percentage change): **LDL-c reduction from baseline to 16 weeks:** rosuva 10 to 40 mg: ─52.3% atorva 10 to 80 mg: ─45.5% Difference: ─6.7% (95% CI ─8.8%, ─4.7%; p<0.0001) **HDL-c increase from baseline to 16 weeks:** rosuva 10 to 40 mg: 5.3% atorva 10 to 80 mg: 4.0% Difference: 1.3% (95% CI ─1.3%, 3.8%; p NS) **Trig reduction from baseline to 16 weeks:** rosuva 10 to 40 mg: ─21.2% atorva 10 to 80 mg: ─21.1% Difference: ─0.1% (95% CI ─5.6%, ─5.3%; p NS)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Berne et al, 2005 **URANUS** R, DB, MC, not ITT 469 patients randomized 16 weeks Supported by AstraZeneca	**Overall adverse events:** rosuva: 51% atorva: 53% **Serious adverse events:** rosuva: 0.8% atorva: 3.4% **Withdrawals due to adverse events:** rosuva: 1.3% atorva: 3.0% No cases of myopathy; myalgia in 3.4% of patients overall; no clinically important elevations in CK.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Blasetto et al, 2003; Shepherd et al, 2003 R, DB, MC 5 trials prospectively designed to allow pooling 1687 patients randomized (n=394 rosuva 5 mg, 392 rosuva 10 mg, 396 atorva 10 mg, 250 simva 20 mg, 255 prava 20 mg) 12 weeks Supported by AstraZeneca	Men and women age 18 or older with LDL-c ≥ 160 mg/dL and <250 mg.dL and triglyceride levels ≤ 400 mg/dL Mean baseline LDL-c 3 pooled trials of rosuva vs atorva: rosuva 5mg: 188 mg/dL rosuva 10mg: 185 mg/dL atorva 10mg: 187 mg/dL 2 pooled trials of rosuva vs prava and simva: rosuva 5mg: 189 mg/dL rosuva 10mg: 187 mg/dL simva 20mg: 188 mg/dL prava 20mg: 189 mg/dL	Rosuva 5 mg or 10 mg; atorva 10 mg; simva 20 mg; prava 20 mg	**3 pooled trials of rosuva vs atorva:** LDL-C reduction from baseline at week 12: rosuva 5mg: 41.9% (p<0.001 vs atorva); rosuva 10mg: 46.7% (p<0.001 vs atorva); atorva 10mg: 36.4% HDL-c increase from baseline at week 12: rosuva 5mg: 8.2% (p<0.01 vs atorva); rosuva 10mg: 8.9% (p<0.001 vs atorva); atorva 10mg: 5.5% Trigs decrease from baseline at week 12: rosuva 5mg: 16.4%; rosuva 10mg: 19.2%; atorva 10mg: 17.6% (NS) Achieved ATP-III LDL-c goal at week 12: rosuva 10 mg: 76% atorva 10 mg: 53% (p<0.001) **2 pooled trials of rosuva vs prava and simva:** LDL-C reduction from baseline at week 12: rosuva 5mg: 40.6% (p<0.001 vs simva and prava); rosuva 10mg: 48.1% (p<0.001 vs simva and prava); prava 20mg 27.1%; simva 20mg 35.7% HDL-c increase from baseline at week 12: rosuva 5mg: 6.9%; rosuva 10mg: 9.1% (p<0.05 vs simva and prava); prava 20mg 6.2%; simva 20mg 6.2% Trigs decrease from baseline at week 12: rosuva 5mg: 14.9%; rosuva 10mg: 20.2% (p<0.01 vs simva and prava); prava 20mg 12.2%; simva 20mg 12.4%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Blasetto et al, 2003; Shepherd et al, 2003 R, DB, MC 5 trials prospectively designed to allow pooling 1687 patients randomized (n=394 rosuva 5 mg, 392 rosuva 10 mg, 396 atorva 10 mg, 250 simva 20 mg, 255 prava 20 mg) 12 weeks Supported by AstraZeneca	No information on adverse events. Equivalent doses not compared

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Brown et al. 2002 R, DB, MC, not ITT 477 patients randomized (n= 239 rosuva, 118 prava vs. 120 simva) 52 weeks 3 authors employed by AstraZeneca	Men and women ≥18 years with LDL-c ≥160 and <250 mg/dl, and triglyceride levels <=400 mg/dL Mean baseline LDL-c rosuva 5mg: 187.3 mg/dL rosuva 10mg: 187.0 mg/dL prava: 188.5 mg/dL simva: 188.0 mg/dL	6-week dietary run-in with NCEP Step 1 diet, then: rosuva 5 mg or rosuva 10 mg or prava 20 mg or simva 20 mg for 12 weeks. Then 40-week titration period to reach NCEP (ATP 2) targets or maximum dose of rosuva 80 mg, prava 40 mg or simva 80 mg.	Efficacy analysis for 471 patients. **LDL-c reduction at 12 weeks:** rosuva 5 mg: 39% (p<0.001 vs prava 20 mg; p<0.05 vs simva 20mg) rosuva 10 mg: 47% (p <0.001 vs prava 20 mg, ≤0.001 vs simva 20 mg) prava 20 mg: 27% simva 20 mg: 35% **HDL increase at 12 weeks:** rosuva 5 mg: 8.2% rosuva 10 mg: 11.9% (p<0.05 vs prava 20 mg) prava 20 mg: 8% simva 20 mg: 9% **Trigs reduction at 12 weeks:** rosuva 5 mg: 17.6% (p<0.05 vs simva 20 mg) rosuva 10 mg: 21.5% (p<0.01 vs prava 20 mg, p≤0.001 vs simva 20 mg) prava 20 mg: 11% simva 20 mg: 10% **Achieved ATP III LDL-c goal at 12 weeks:** rosuva 5 mg: 78% rosuva 10 mg: 88% prava 20 mg: 51% simva 20 mg: 63% (p-values not reported)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Brown et al. 2002 R, DB, MC, not ITT 477 patients randomized (n= 239 rosuva, 118 prava vs. 120 simva) 52 weeks 3 authors employed by AstraZeneca	Withdrawals due to treatment-related adverse events:7 rosuva 5 mg, 7 rosuva 10 mg, 6 prava, 7 simva. 1 serious AE identified with treatment: simva patient with asthenia and chest pain, resolved with no change in treatment. Transient elevations in ALT >3x ULN without symptoms: 2 rosuva 5 mg, 0 rosuva 10 mg, 5 prava, 2 simva Increased laboratory. <u>Equivalent doses not compared</u>

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Davidson et al, 2002 R, DB, MC, PC. 519 patients randomized (n=132 placebo, 129 rosuva 5mg, 130 rosuva 10mg, 128 atorva 10mg) 12 weeks Supported by a grant from AstraZeneca	Men and women age 18 and older with fasting LDL-c ≥ 160 mg/dL and <250 mg/dL and fasting triglycerides ≤ 400 mg/dL, and a score of 28 or less on section 1 of the Eating Pattern Assessment Tool (indicating compliance with NCEP step I diet). Mean baseline LDL-c rosuva 5mg: 188 mg/dL rosuva 10mg: 185 mg/dL atorva 10mg: 186 mg/dL	6-week dietary run-in with NCEP Step 1 diet 12 week trial with NCEP Step 1 diet and rosuvastatin 5 or 10 mg, atorvastatin 10 mg, or placebo once a day	**LDL-c reduction from baseline at week 12:** rosuva 5 mg: 40% (p< 0.01 vs atorva) rosuva 10 mg: 43% (p<0.001 vs atorva) atorva 10 mg: 35% **HDL-c increase from baseline at week 12:** rosuva 5 mg: 13% (p< 0.01 vs atorva) rosuva 10 mg: 12% (p< 0.05 vs atorva) atorva 10 mg: 8% **Triglycerides reduction from baseline at week 12:** rosuva 5 mg: 17% rosuva 10 mg: 19% atorva 10 mg: 19%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Davidson et al, 2002 R, DB, MC, PC. 519 patients randomized (n=132 placebo, 129 rosuva 5mg, 130 rosuva 10mg, 128 atorva 10mg) 12 weeks Supported by a grant from AstraZeneca	Withdrawals due to adverse events: 4 (3.1%) atorva, 6 (4.7%) rosuva 5mg, 4 (3.1%) rosuva 10mg. No clinically significant elevations in CK or ALT/AST. Types and incidences of adverse events similar across all treatment groups. Adverse events related to study treatment: 18 rosuva 5mg (14.1%), 17 rosuva 10mg (13.2%), 25 atorva (19.7%). Most frequently reported were constipation, flatulence, nausea, and myalgia. Serious adverse events in 5 (3.9%) atorva patients (angina, coronary vascular disorder, tooth disorder, pathologic fracture, hypertension, cholelithiasis, ileus, and pneumonia); 3 (2.3%) rosuva 5mg patients (angina, heart failure, meningitis, bone disorder, infection), 0 in rosuva 10mg group. No serious adverse event was considered by the investigators to be related to study drug. <u>Equivalent doses not compared</u>

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Ferdinand et al, 2006 R, Open, MC 774 patients randomized 6 week treatment period Supported by AstraZeneca	African-American men and women aged 18 or older who were diagnosed with type IIa or IIb hypercholesterolemia. After dietary lead-in, patients were eligible for randomizaton if they had fasting LDL-C >=160 mg/dl and <=300 mg/dl and triglycerides <400 mg/dl. Mean baseline LDL-c: 190.6 mg/dL	After a 6 week dietary lead-in, treatment for 6weeks: rosuva 10 or 20 mg or atorva 10 or 20 mg	**% LDL-c reduction from baseline at 6 weeks:** rosuva 10: –37.1% (p<0.017 vs atorva 10) rosuva 20: –45.7% (p<0.017 vs atorva 20) atorva 10: –31.8% atorva 20: –38.5% % HDL-c increase from baseline at 6 weeks: rosuva 10: +7.0% (p<0.017 vs atorva 20) rosuva 20: +6.5% atorva 10: +5.6% atorva 20: +3.7% % trig reduction from baseline at 6 weeks: rosuva 10: –16.0% rosuva 20: –20.9% atorva 10: –17.1% atorva 20: –19.6% % of patients meeting ATP III goal at 6 weeks: rosuva 10: –66.1% rosuva 20: –78.8% atorva 10: –58.1% atorva 20: –61.8%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Ferdinand et al, 2006 R, Open, MC 774 patients randomized 6 week treatment period Supported by AstraZeneca	**Any adverse event:** rosuva 10/20: 34.4% atorva 10/20: 33.6% **Myalgia:** rosuva 10: 2.6% rosuva 20: 3.6% atorva 10: 2.6% atorva 20: 1.0% Withdrawals due to AEs: rosuva 10/20: n=13 (3.3%) atorva 10/20: n=5 (1.3%) No deaths, myopathy, or rhabdomyolysis

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Fonseca et al, 2005 R, Open, MC 1124 patients randomized 12 week treatment period Supported by AstraZeneca	Patients age 18 and older with primary hypercholesterolemia, with fasting LDL-C =>5 mg/dL above their NCEP ATP III goal by risk category. Mean baseline LDL-c: Statin-naïve: 173 mg/dL Switched: 163 mg/dL	Statin-naïve patients completed a 6-week dietary counseling period before entering the study, while switched patients entered the study directly with no dietary run-in. Treatment for 12 weeks: rosuva 10 mg (n=561) or atorva 10 mg (n=563)	**% LDL-c reduction from baseline at 12 weeks (statin-naïve patients):** rosuva 10 (n=358): –40.9% atorva 10 (n=383): –34.8% (p<0.001) **% LDL-c reduction from baseline at 12 weeks (switched patients):** rosuva 10 (n=173): –35.3% atorva 10 (n=161): –27.5% (p<0.01) % HDL-c increase from baseline at 12 weeks (statin-naïve patients): rosuva 10 (n=358): 3.9% atorva 10 (n=383): 0.9% (p<0.05) % HDL-c increase from baseline at 12 weeks (switched patients): rosuva 10 (n=173): 2.5% atorva 10 (n=161): 0.0% (NS) % of patients achieving NCEP ATP III goal at 12 weeks: rosuva 10 (n not reported): 71.2% atorva 10 (n not reported): 61.4% (p<0.001)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Fonseca et al, 2005 R, Open, MC 1124 patients randomized 12 week treatment period Supported by AstraZeneca	**Treatment-emergent adverse events:** rosuva 10: 25.7% atorva 10: 21.2% **Serious adverse events:** rosuva 10: 1.2% atorva 10: 2.0% **Discontinuations due to adverse events:** rosuva 10: 4.8% atorva 10: 1.8% No cases of rhabdomyolysis, myopathy or renal insufficiency were observed.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Jones et al, 2003 (STELLAR) R, OL, MC 2431 patients randomized (n=643 rosuva, 641 atorva, 655 simva, 492 prava) 6 weeks Supported by AstraZeneca	Men and nonpregnant women age 18 or older with LDL-c >=160 and <250 mg/dL. Triglyceride levels <400 mg/dL. Mean baseline LDL-c (mg/dL) rosuva: 10mg 188; 20mg 187; 40mg 194 atorva: 10mg 189; 20mg 190; 40mg 189; 80mg 190 simva: 10mg 189; 20mg 189; 40mg 187; 80mg 190 prava: 10mg 189; 20mg 187; 40mg 190	Rosuvastatin 10, 20, 40, or 80 mg; atorvastatin 10, 20, 40, or 80 mg; simvastatin 10, 20, 40, or 80 mg; pravastain 10, 20, or 40 mg all once daily for 6 weeks.	**LDL-c reduction from baseline at week 6:** rosuva: 10mg 45.8%; 20mg 52.4%; 40mg 55% atorva: 10mg 36.8%; 20mg 42.6^; 40mg 47.8%; 80mg 51.1% simva: 10mg 28.3%; 20mg 35.0%; 40mg 38.8%; 80mg 45.8% prava: 10mg 20.1%; 20mg 24.4%; 40mg 29.7% equivalent doses: rosuva 10mg > atorva 20mg (p=0.026) and simva 40mg (p<0.001) rosuva 20mg > atorva 40mg (p<0.002) and simva 80mg (p<0.001) rosuva 40mg >atorva 80mg (p=0.006) **HDL-c increase from baseline at week 6:** rosuva: 10mg 7.7%; 20mg 9.5%; 40mg 9.6% atorva: 10mg 5.7%; 20mg 4.8%; 40mg 4.4% 80mg 2.1% simva: 10mg 5.3%; 20mg 6.0%; 40mg 5.2%; 80mg 6.8% prava: 10mg 3.2%; 20mg 4.4%; 40mg 5.6% equivalent doses: rosuva 10 mg = atorva 20 mg rosuva 10mg = simva 40 mg rosuva 20 mg > atorva 40mg (p<0.002) rosuva 20 mg = simva 80 mg **Trigs reduction from baseline at week 6:** rosuva: 10mg 19.8%; 20mg 23.7%; 40mg 26.1% atorva: 10mg 20.0%; 20mg 22.6%; 40mg 26.8%; 80mg 28.2% simva: 10mg 11.9%; 20mg 17.6%; 40mg 14.8%; 80mg 18.2%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Jones et al, 2003 (STELLAR) R, OL, MC 2431 patients randomized (n=643 rosuva, 641 atorva, 655 simva, 492 prava) 6 weeks Supported by AstraZeneca	Withdrawals due to adverse events: 23/643 rosuva (3.6%), 25/641 atorva (3.9%), 19/655 simva (2.9%), 11/492 prava (2.2%); 46% of all patients reported adverse events, 29 patients had serious adverse events. 2 rosuva 80mg patients developed acute renal failure of uncertain etiology. Most common adverse events pain, pharyngitis, myalgia, headache. <u>Dose equivalence (LDL-c lowering)</u> rosuva 10mg > atorva 20mg and simva 40mg rosuva 20mg > atorva 40mg and simva 80mg rosuva 40mg >atorva 80mg

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Jukema et al, 2005 R, open-label, multicenter 461 patients randomized 18 week treatment period Supported by AstraZeneca	Men and women aged 40 to 80 years with established cardiovascular disease, fasting HDL-c <40 mg/dL at visit 1 and baseline, and triglycerides <=400 mg/dL at visit 1. Mean baseline LDL-c: 141 mg/dL	After a 6 week dietary lead-in, treatment for the first 6 weeks: rosuva 10 mg (n=230) or atorva 20 mg (n=231) At week 6, dosages increased for 6 weeks: rosuva 20 mg or atorva 40 mg At week 12, dosages increased for 6 weeks: rosuva 40 mg or atorva 80 mg	**% LDL-c reduction from baseline at 6, 12, and 18 weeks (p vs atorva):** rosuva 10/20/40: –44.0% (p<0.05)/–50.4% (p<0.01)/–55.3% (p<0.0001) atorva 20/40/80: –38.4%/–45.1%/–48.1% **% HDL-c increase from baseline at 6, 12, and 18 weeks:** rosuva 10/20/40: 3.9%/5.5%/4.7% atorva 20/40/80: 4.1%/3.1%/2.7% All NS **% trig reduction from baseline at 6, 12, and 18 weeks (p vs atorva):** rosuva 10/20/40: –29.2% (p<0.05)/–32.2%/–35.4% atorva 20/40/80: –23.9%/–27.3%/–31.6%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Jukema et al, 2005 R, open-label, multicenter 461 patients randomized 18 week treatment period Supported by AstraZeneca	Occurrence of deaths, serious adverse events and withdrawals due to adverse events was low, with no differences noted between treatment groups (data not reported). 1 death in rosuva group (sudden death), 1 in atorva (liver metastasis), not considered related to study treatment. 2 treatment related serious adverse events in atorva group (both high creatine kinase activities)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Olsson et al, 2002 R, DB, MC 412 patients randomized (n=138 rosuva 5mg, 134 rosuva 10mg, 140 atorva 10mg) 52 weeks Supported by a grant from AstraZeneca	Men and women age 18 and older with LDL-c level between 160 and <250 mg/dL and an EPAT score 28 or less. <u>Mean baseline LDL-c</u> rosuva 5mg: 188.0 mg/dL rosuva 10mg:185.9 mg/dL atorva 10mg: 188.1mg/dL	5 or 10 mg rosuva or 10 mg atorva for 12 weeks, then titrated up to 80 mg if NCEP ATP-II LDL-c goal not met, for a total of 52 weeks.	**LDL-c reduction from baseline at 12 weeks:** rosuva 5 mg: 46% (p<0.001 vs atorva) rosuva 10 mg: 50% (p<0.001 vs atorva) atorva 10 mg: 39% **Percentage of patients achieving NCEP ATP-II LDL-c goal at 12 weeks:** rosuva 5 mg: 86% rosuva 10 mg: 89% atorva 10 mg: 73% (NS) **Percentage of patients achieving NCEP ATP-II LDL-c goal at 52 weeks:** rosuva 5 mg: 88% rosuva 10 mg: 98% atorva 10 mg: 87% (NS) **HDL-c increase from baseline at 12 weeks:** rosuva 5 mg: 6% (NS vs atorva) rosuva 10 mg: 8% (NS vs atorva) atorva 10 mg: 6% **Trigs reduction from baseline at 12 weeks:** rosuva 5 mg: 15% (NS vs atorva) rosuva 10 mg: 19% (NS vs atorva) atorva 10 mg: 16%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Olsson et al, 2002 R, DB, MC 412 patients randomized (n=138 rosuva 5mg, 134 rosuva 10mg, 140 atorva 10mg) 52 weeks Supported by a grant from AstraZeneca	Adverse events considered to be treatment related occurred in 29% of rosuva 5mg, 27% rosuva 10mg, and 35% atorva 10mg patients. Most frequently reported were myalgia and GI complaints. Serious adverse events leading to withdrawal: rectal hemorrhage (rosuva 10mg(, serum creatinine elevation (rosuva 10mg), ALT/AST elevations (atorva 10mg). Total 28 withdrawals due to adverse events. Of these 5 rosuva 5mg, 5 rosuva 10mg, and 8 atorva 10mg had adverse events considered treatment-related. <u>Equivalent doses not compared</u>

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Paoletti et al. 2001 R, DB, MC, ITT 502 patients randomized 12 weeks Sponsored by and one author employed by AstraZeneca	Men and women age≥18 years with hypercholesterolaemia, fasting LDL-c ≥160 and <250 mg/dl, fasting trig ≤400 mg/dl Mean baseline LDL-c 189 mg/dl	Screening phase, then randomization to: rosuva 5 or 10 mg prava 20 mg or simva 20 mg or for 12 weeks	Efficacy analysis for 495 patients. **LDL-c reduction from baseline at 12 weeks:** rosuva 5 mg: 42% (p<0.001 vs prava, p<0.005 vs simva) rosuva 10mg: 49% (p<0.001 vs prava, p<0.001 vs simva) prava: 28% simva: 37% **HDL-c increase from baseline at 12 weeks:** rosuva 5 mg: 6% rosuva 10mg: 7% prava: 4% simva: 4% (NS) **Trigs reduction from baseline at 12 weeks:** rosuva 5 mg: 12% rosuva 10mg: 18% prava: 13% simva: 14% (NS) **Achieved NCEP ATP II LDL-c goal:** rosuva 5 mg: 71% rosuva 10mg: 87% prava: 53% simva: 64% (NS)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Paoletti et al. 2001 R, DB, MC, ITT 502 patients randomized 12 weeks Sponsored by and one author employed by AstraZeneca	Serious AEs in 4 (3.5%) rosuva 10 mg patients (life-threatening cerebral hemorrhage, life threatening myocarcdial infarction, syncope, and cholecystitis plus cholelithiasis). No serious AEs considered by the investigator to be related to study treatment. Withdrawal due to AEs: rosuva 5 mg: 2 (1.6%) chest pain and infection, migraine rosuva 10 mg: 6 (5.2%) cerebral hemorrhage, diarrhea, CK increase and myalgia, headache and edema, urticaria) prava: 3 (2.2%) vasodilation and abdominal pain, dyspepsia, conjunctivitis) simva: 1 (0.8%) abdominal pain. ADEs: prava 19/136 (14%) vs simva 23/129 (18%). Most common ADEs: constipation (3 vs. 2), diarrhea ((1 vs. 1),, dyspepsia (2 vs. 3), pruritus (1 vs. 4), abdominal pain (2 vs. 4). ALT elevation in 2 simva, 3 rosuva 5 mg, and 1 rosuva 1 mg patients. No clinically significant ALT or CK elevations. Equivalent doses not compared

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Schneck et al, 2003 R, DB, MC 374 patients randomized (n=165 atorva, 209 rosuva) 6 weeks Supported by AstraZeneca Pharmaceuticals	Men and women age 18 and older with hypercholesterolemia and without active arterial disease within 3 months of study entry or uncontrolled hypertension; LDL-c ≥ 160 mg/dL but <250 mg/dL, triglycerides <400 mg/dL, and Eating Pattern Assessment Tool (to assess adherence to NCEP Step I diet) score of 28 or less. Mean baseline LDL-c atorva: 10mg 38.2%; 20mg:43.3%; 40mg 48.4%; 80 mg 53.5% rosuva: 5mg 41.5%;	Atorva 10, 20, 40, or 80 mg qd or rosuvastatin 5, 10, 20, 40, or 80 mg qd for 6 weeks.	**Reduction in LDL-c from baseline at 6 weeks:** atorva: 10mg 38.2%; 20mg:43.3%; 40mg 48.4%; 80 mg 53.5% rosuva: 5mg 41.5%; 10mg 46.6%; 20mg 51.7%; 40mg 56.8%; 80mg 61.9% (p<0.001 difference vs atorva across dose range) **Increase in HDL-c from baseline at 6 weeks:** atorva: 10mg 5.0%; 20mg 7.6%; 40mg 4.1%; 80mg 2.1% rosuva: 5mg 7.4%; 10mg 6.0%; 20mg 9.1%; 40mg: 12.3%; 80mg 9.6% (NS) **Reduction in trigs from baseline at 6 weeks:** atorva: 10mg: 17.5%; 20mg 25.6%; 40mg 27.2%; 80mg 34.5% rosuva: 5mg 23.1%; 10mg 22.1%; 20mg 18.4%; 40mg 25.7%; 80mg 19.7% (NS)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Schneck et al, 2003 R, DB, MC 374 patients randomized (n=165 atorva, 209 rosuva) 6 weeks Supported by AstraZeneca Pharmaceuticals	Any adverse event: 51.2% rosuva vs 47.9% atorva (NS); no consistent relation in occurrence of individual treatment-emergent adverse events to doses of either drug. Withdrawals due to adverse events infrequent (1 patient each in rosuva 10 mg, 20 mg, 80 mg groups, atorva 10 mg 40 mg, and 80 mg groups). Most common adverse events pharyngitis, headache, and pain. <u>Dose equivalence (LDL-c lowering)</u> rosuva 5mg > atorva 20mg rosuva 10mg > atorva 20mg rosuva 20mg > atorva 40mg rosuva 40mg > atorva 80mg

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)

Schuster et al. 2004
R,OL,MC,ITT
 	
5-arm trial that included statin switching (to rosuvastatin) at 8 weeks
 	
3140 patients randomized
16 weeks of treatment
 	
Sponsored by Astra Zeneca
	Patients aged >=18 years, with CHD or other atherosclerotic disease, type 2 diabetes, a CHD risk >20% over 10 years, with LDL-c levels>=115 mg/dL and trig <400 mg/dL; LDL-c measurements had to be within 15% of each other during the lead-in period.
	
	Baseline LDL-c levels:
	Rosuv 10 mg: 164.9 mg/dL
	Atorva 10 mg: 162.2 mg/dL
	Atorva 20 mg: 167.5 mg/dL
	Simva 20 mg: 165.5 mg/dL
	Prava 40 mg: 163.8 mg/dL
		6 week dietary lead-in phase, then randomization to 5 arm trial system (drug a for 8 weeks then drug b or c for eight additional weeks):
		rosuv 10 mg (n=538), to rosuv 10 mg (n=521);
		
		atorva 10 mg (n=529), to rosuv 10 mg (n=276) or atorva 10 mg (n=240);
		
		atorva 20 mg (n=925), to rosuv 10 mg (n=293), rosuv 20 mg (n=305), or atorva 20 mg (n=299);
		
		simva 20 mg (n=543), to rosuv 10 mg (n=277) or simva 20 mg (n=250);
		
		prava 40 mg (n=521), to rosuv 10 mg (n=253) or prava 40 mg (n=253).
			% LDL-c reduction from baseline to 8 weeks:
			Rosuv 10 mg (n=521): -47.0%
			Atorva 10 mg (n=240): -37.2%
			Atorva 20 mg (n=299): -43.7%
			Simva 20 mg (n=250): -35.4%
			Prava 40 mg (n=253): -31.0%
			(p<0.0001 for all comparisons vs rosuva 10 mg)
			% HDL-c increase from baseline to 8 weeks:
			Rosuv 10 mg (n=521): +9.2%
			Atorva 10 mg (n=240): +6.8% (p<0.01 vs rosuva 10 mg)
			Atorva 20 mg (n=299): +5.7% (p<0.0001 vs rosuva 10 mg)
			Simva 20 mg (n=250): +8.0% (NS vs rosuva 10 mg)
			Prava 40 mg (n=253): +7.6% (NS vs rosuva 10 mg)
			% trig reduction from baseline to 8 weeks:
			Rosuv 10 mg (n=521): -18.9% (p<0.01 vs rosuva 10 mg)
			Atorva 10 mg (n=240): -15.9% (NS vs rosuva 10 mg)
			Atorva 20 mg (n=299): -18.3% (NS vs rosuva 10 mg)
			Simva 20 mg (n=250): -13.5% (p<0.01 vs rosuva 10 mg)
			Prava 40 mg (n=253): -10.5% (p<0.0001 vs rosuva 10 mg)
			Proportion of patients achieving the ATP III LDL-c goals at week 8:
			Rosuv 10mg (n=538): 80%
			Atorva 10 mg (n=529): 63% (p<0.0001 vs rosuva 10 mg)
			Atorva 20 mg (n=925): 74% (p<0.01 vs rosuva 10 mg)
			Simva 20 mg (n=543): 54% (p<0.0001 vs rosuva 10 mg)
			Prava 40 mg (n=521): 45% (p<0.0001 vs rosuva 10 mg)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Schuster et al. 2004 **R,OL,MC,ITT** 5-arm trial that included statin switching (to rosuvastatin) at 8 weeks 3140 patients randomized 16 weeks of treatment Sponsored by Astra Zeneca	"Occurrence of deaths, serious adverse events (SAE's), and withdrawals due to adverse events (AE's) were low, with no differences noted among the treatment groups." 8 patients died during the trial, but those deaths occurred from "causes that would be expected in such a patient population (i.e., cardivascular events=4, malignancy=2, pneumonia=1, and subdural hematoma=1". No treatment-related AE's leading to death nor any treatment-related SAE's are reported. SAE's or AE's are not always categorized by drug type. Myalgia - reported in 1.9% of patients in period 1 and 0.9% of patients in period 2. No cases of myopathy were reported (creatine kinase >10 times ULN and muscle symptoms). Atorva 20 mg and rosuv 10 mg each had 1 case of asymptomatic increase in creatine kinase >10 times ULN; both resolved during continued study treatment. No patients had increases in hepatic transaminases >3 times ULN and >= consecutive measurements.

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Schwartz et al, 2004 R, DB, MC 382 patients randomized 24 week treatment period Supported by AstraZeneca	Patients aged >18 years, with LDL-C levels >=160 and< 250 mg/dL, and trig levels <=400 mg/dL, and documented atherosclerosis, Type 2 diabetes, or both, assessed. Patients with score of <=28 on Eating Pattern Assessment Tool, fasting LDL-C levels >160mg/dL and trig levels <400 mg/dL at 2 consecutive measurements were randomized. Mean baseline LDL-c levels: Rosuv 5/20/80: 188 mg/dL Rosuv 10/40/80: 186 mg/dL Atorv 10/40/80: 188 mg/dL	After a 6 week dietary lead-in, treatment for the first 12 weeks: rosuv 5 mg (n=127) once daily or rosuv 10 mg (n=128) once daily or atorv 10 mg (n=128) once daily If LDL-c remained >50 mg/dl, then the doses were uptitrated at weeks 12 and 18 to: rosuv 5 mg became 20 mg and then 80 mg (rosuv 5/20/80) rosuv 10 mg became 40 mg and then 80 mg (rosuv 10/40/80) atorv 10 mg became 40 mg and then 80 mg (atorv 10/40/80)	**% LDL-c reduction from baseline at 12 and 18 weeks:** rosuv 5/20/80: -39.8%(p<0.01), -51.6%(p<0.01 vs atorv) rosuv 10/40/80: -47.1%(p<0.001), -58.8%(p<0.001 vs atorv) atorv 10/40/80: -35.0%, -47.2% **% HDL-c increase at 12 and 18 weeks:** rosuv 5/20/80: +6.6% (p<0.01),+8.3%(p<0.001 vs atorv) rosuv 10/40/80: +7.7%(p<0.001),+10%(p<0.001 vs atorv) atorv 10/40/80: +2.7%,+1.4% **% trig reduction at 12 and 18 weeks:** (no p-values stated for any of these %) rosuv 5/20/80: -17.4%, -20.7% rosuv 10/40/80: -19.8%, -22.9% atorv 10/40/80: -17.8%, -22.1% **% of patients meeting the ATP III LDL-c goal of <100 mg/dL at 12 weeks:** Rosuv 5 mg/d: 34.6% (p=0.002 vs atorv) Rosuv 10mg/d: 59.4% (p<0.001 vs atorv) Atorv 10 mg/d: 16.5% **% of patients meeting the ATP III LDL-c goal of <100 mg/dL at 18 weeks:** Rosuv 20 mg/d: 72.4% (p=0.035 vs atorv) Rosuv 40mg/d: 88.3% (p<0.001 vs atorv) Atorv 40 mg/d: 60.6%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Schwartz et al, 2004 R, DB, MC 382 patients randomized 24 week treatment period Supported by AstraZeneca	"Although adverse events were frequently reported in these high-risk patients, they were generally mild and not attributed to trial medication." Most common AEs pharyngitis, pain, myalgia **Any adverse event (AE):** rosuv 5/20/80: n=116 (91%) rosuv 10/40/80: n=113 (88%) atorv 10/40/80: n=101 (80%) **AEs considered treatment-related:** rosuv 5/20/80: n=36 (28%) rosuv 10/40/80: n=38 (30%) atorv 10/40/80: n=35 (28%) **Serious AEs:** rosuv 5/20/80: n=12 (9%) rosuv 10/40/80: n=8 (6%) atorv 10/40/80: n=7 (6%) **Withdrawals due to AEs:** rosuv 5/20/80: n=5 (4%) rosuv 10/40/80: n=7 (6%) atorv 10/40/80: n=6 (5%)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Stalenhoef et al. 2005 **R, DB, MC, PC, not ITT** **(COMETS)** 401 patients randomized 12 weeks Supported by AstraZeneca	Men and women >=18 years with the metabolic syndrome, defined by presence of at least 3 of the following: abdominal obesity, TG >=150 mg/dL, HDL-c <40mg/dL for men and <50mg/dL for women, blood pressure >=130/85 or receiving antihypertensive treatment, and fasting blood glucose >=110 mg/dL. Also required to have LDL-c >=130 mg/dL and additional multiple risk factors conferring a 10-year CHD risk score of >10%. Patients with diabetes excluded.	After 4-week dietary lead-in rosuva 10 mg or atorva 10 mg or placebo for 6 weeks, then atorva rosuva 10 mg or atorva 20 mg for 6 weeks (placebo group also switched to rosuva 20 mg)	Efficacy analysis for 397 patients: **LDL-c reduction from baseline to 6 weeks:** rosuva 10 mg: –42.7% (p<0.001 vs atorva) atorva 10 mg: –36.6% placebo: –0.3% **LDL-c reduction from baseline to 12 weeks:** rosuva 10 mg: –48.9% (p<0.001 vs atorva) atorva 10 mg: –42.5% **HDL-c increase from baseline to 6 weeks:** rosuva 10 mg: 9.5% (p<0.01 vs atorva) atorva 10 mg: 5.1% placebo: 1.1% **HDL-c increase from baseline to 12 weeks:** rosuva 10 mg: 10.4% (p<0.01 vs atorva) atorva 10 mg: 5.8% **Trig reduction from baseline to 6 weeks:** rosuva 10 mg: –19.1% (NS) atorva 10 mg: –20.9% placebo: –2.8% **Trig reduction from baseline to 12 weeks:** rosuva 10 mg: –22.9% (NS) atorva 10 mg: –25.2% **Patients meeting NCEP ATP III goal at 6 weeks:** rosuva 10 mg: –83% (p<0.05 vs atorva) atorva 10 mg: –72% placebo: –10% **Patients meeting NCEP ATP III goal at 12 weeks:** rosuva 10 mg: –91% (p<0.001 vs atorva) atorva 10 mg: –79%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Stalenhoef et al. 2005 **R, DB, MC, PC, not ITT** **(COMETS)** 401 patients randomized 12 weeks Supported by AstraZeneca	**Overall adverse events:** rosuva (weeks 1-6) 25.2%; (weeks 6-12) 22.2% atorva: (weeks 1-6) 25.3%; (weeks 6-12) 20.7% **Serious adverse events:** rosuva: (weeks 1-6) 0%; (weeks 6-12) 0.6% atorva: (weeks 1-6) 1.9%; (weeks 6-12) 0.7% **Withdrawals due to adverse events:** rosuva: (weeks 1-6) 1.2%; (weeks 6-12) 1.3% atorva: (weeks 1-6) 1.9%; (weeks 6-12) 0.7%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Strandberg et al, 2004 **R (2:1), OL, MC, 2-arm study, ITT** 1024 patients randomized (n=686 to rosuv 10 mg/d, n=338 to atorv 10 mg/d) 12 weeks Supported by a grant from AstraZeneca	Men and women >=18 years with LDL-c level >135 mg/dL for statin-naïve patients or >120 mg/dL in patients using the starting dose of another lipid-lowering drug. They had to be at high risk for CHD and have primary hypercholesterolemia. <u>Mean baseline LDL-c</u> rosuva 10mg: 174 mg/dL atorva 10mg: 170 mg/dL	rosuv 10 mg/d atorv 10 mg PO OD optional extension period for rosuv pts who did not have access to drug commercially, and for atorv pts who did not achieve the 1998 JTF goal for LDL-c after 12 weeks. Rosuv could be up-titrated at 12 wk intervals to 20 mg/d and then to 40 mg/d to achieve the 1998 JTF LDL-c goal (1998 target of <116 mg/dL; JTF 2003 target of <97 mg/dL).	Efficacy analysis for 911 patients (rosuv 10mg/d, n= 627; atorv 10mg/d, n= 284) **LDL-c levels at 12 weeks:** rosuv 10 mg: 89 mg/dL atorv 10 mg: 104 mg/dL % **LDL-c reduction from baseline at 12 weeks:** rosuv 10 mg: -46.92 % change (p< 0.05 vs. atorv) atorv 10 mg: -38.07 % change from baseline <u>% </u>**HDL-c increase 12 weeks after baseline:** rosuv 10 mg: 4.00 % increase (p<0.05 vs. atorv) atorv 10 mg: 1.88 increase **% decrease in trig levels at 12 weeks:** rosuv 10 mg: -14.55% (p<0.05 vs. atorv) atorv 10 mg: -13.98% **% patients reaching JTF LDL-c targets after 12 weeks:** (1998 target of <116 mg/dL; 2003 target of <97 mg/dL) rosuv: 83.4%; ~73% (p<0.001 vs. atorv) atorv: 68.3%; ~51.1%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Strandberg et al, 2004 **R (2:1), OL, MC, 2-arm study, ITT** 1024 patients randomized (n=686 to rosuv 10 mg/d, n=338 to atorv 10 mg/d) 12 weeks Supported by a grant from AstraZeneca	**Patients experiencing any AE (estimated from graph)**: Rosuv ~38% (n=261) Atorv ~37% (n=125). Rosuv: 1 patient had melena (later diagnosed as duodenal ulcer); 1 patient having a history of peptic ulcer disease and receiving concmitant treatment with a NSAID (diclofenac) had vomiting; 1 patient had myopathy accompanied by increased creatine levels Atorv: 1 patient had proteinuria found to be non-treatment related **AE's in rosuv vs. atorv:** *n=AE incidence (%)/ n=led to discontinuation (%)* muscle pain/myalgia: 18(2.6%)/ 13(1.9%) vs. 4(1.2%)/ 3(0.9%) nausea: 12(1.7%)/ 7(1.0%) vs.5(1.5%)/ 3(0.9%) increased ALT: 11(1.6%)/ 2(0.3%) vs. 1(0.3%)/ 0(0%) increased AST: 8(1.2%)/ 0(0%) vs. 3(0.9%)/ 0(0%) increased creatine kinase (CK): 6(0.9%)/ 0(0%) vs. 6(1.8%)/ 1(0.3%) headache: 6(0.9%)/ 2(0.3%) vs. 4(1.2%)/ 3(0.9%) **Total withdrawals due to AEs (some patients experienced >1 adverse event):** Rosuv: n=24 (3.5%) Atorv: n=10 (3.0%)

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Inclusion Criteria/ Patient Population	Intervention	Results (mean changes in lipoprotein levels)
Wolffenbuttel et al. 2005 R, Open-label, MC 263 patients randomized (N=263) 18 week treatment period Supported by AstraZeneca	Men and women with type 2 diabetes who had received treatment for diabetes for at least 3 months, older than 18 years, with fasting LDL-c concentrations of >=130 mg/dL in statin-naïve patients or >115 to <=193 in patients who had been taking a statin within the previous 4 weeks. Normal to moderately elevated trig levels, and in acceptable metabolic control. Mean baseline LDL-c: rosuva: 163.3 atorva: 171.0	After a 6-week dietary lead-in, treatment for the first 6 weeks: rosuva 10 mg or atorva 20 mg At week 6, dose increased for 6 weeks: rosuva 20 mg or atorva 40 mg At week 12, dose increased for 6 weeks: rosuva 40 mg or atorva 80 mg	**% LDL-c reduction from baseline at 6, 12, and 18 weeks (p vs atorva):** rosuva 10/20/40: 45.9% (p<0.05)/50.6% (p<0.05)/53.6% (p<0.01) atorva 20/40/80: 41.3%/45.6%/47.8% **% HDL-c increase from baseline at 6, 12, and 18 weeks (p vs atorva):** rosuva 10/20/40: 0.7%/0.1%/–1.1% atorva 20/40/80: –1.2%/–2.3%/–2.8% All NS **% trig reduction from baseline at 6, 12, and 18 weeks:** rosuva 10/20/40: 18.8%/23.7%/22.7% atorva 20/40/80: 16.3%/17.6%/23.7% All NS **% of patients achieving LDL-c goals at 6, 12, and 18 weeks (p vs atorva):** Patients reaching LDL-c <100.5 (ADA guideline) rosuva 10/20/40: 81.5%/83.8%/91.5% (p<0.05) atorva 20/40/80:73.5%/78.8%/81.1% Patients reaching LDL-c <96.8 (new EAS guideline) rosuva 10/20/40: 77.7%/83.1%/90.0% (p<0.05) atorva 20/40/80:70.5%/76.5%/78.0%

Evidence Table 1. Trials comparing LDL-c lowering/HDL-c raising abilities of 2 or more statins

Clinical Trial	Safety/Comments
Wolffenbuttel et al. 2005 R, Open-label, MC 263 patients randomized (N=263) 18 week treatment period Supported by AstraZeneca	**Overall adverse events:** rosuva: 47% atorva: 50% **Serious adverse events:** rosuva: 5% atorva: 2% **Withdrawals due to adverse events:** rosuva: 7% atorva: 8% Myalgia was the most frequently reported adverse event (5% rosuva, 11% atorva). No myopathy. One atorva patient developed abnormality in ALT (>3X ULN)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
Studies in outpatients						
ALLHAT Officers and Coordinators 2002 Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)	Randomized, open-label vs. usual care, intention-to-treat analysis	10,355 people age 55+ with stage 1 or 2 hypertension and 1+ CHD risk factor; for those with no known CHD: LDL-C 120-189 mg/dL; for those with known CHD: LDL-C 100-129 mg/dL; triglyceride lower than 350 mg/dL.	Pravastatin 40 mg/day or usual care	4.8 years (max=7.8)	145.55 mg/dL (calculated = 3.73 mmol/L)	**Year 2** - base = 23.8% - usual = 16.5% **Year 4** - base = 28.2% - usual = 16.7% **Year 6** - base = 28.6% - usual = 11.9% (calculated from table - figured different in text)
Asselbergs et al 2004 Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT)	Randomized, active and placebo-controlled, double-blind, single center	864 residents of one city in the Netherlands, ages 28-75 with persistent microalbuminuria, blood pressure <160/100 mm Hg, and no use of antihypertensive medicaiton, and a total cholesterol level <309 mg/dL, or <193 mg/dL in case of previous myocardial infarction, and no use of lipid-lowering medication.	Pravastatin 40 mg or matching placebo and fosinopril 20 mg or matching placebo.	46 $\pm$ 7 months	174 $\pm$ 37	pravastatin vs placebo 3 months: 30% vs % 1 year: 25% vs 3% 2 years: 25% vs 3% 3 years: 25% vs 0% 4 years: 25% vs 3%
Colhoun 2004 Collaborative Atorvastatin Diabetes Study (CARDS)	Randomized, double-blind, placebo-controlled, multicenter	2838 men and women with no history of cardiovascular disease, LDL of 4.14 or lower, fasting triglyceride of 6.78 or less, and at least one of the following: retinopathy, albuminuria, current smoking, or hypertension.	Atorvastatin 10 mg/day or placebo	median 3.9 years	117 +32 mg/dl	36% (95% CI 37% to 35%)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death	All Cause Mortality	Major Coronary Events
Studies in ol					
ALLHAT Officers and Coordinators 2002 Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)	**6-Year Rate** **Fatal CHD & Nonfatal MI** RRR= 9% (11% calculated) ARR= 1.1 events/ 100 ppl p= .16 95% CI = -4-21% NNT= 91	NR	**6-Year Rate** **CVD Deaths** RRR= 1% (3% calculated) ARR= 0.2 events/ 100 ppl p= .91 95% CI = -16-16% NNT= 500 **CHD Deaths** RRR= 1% (5% calculated) ARR= 0.2 events/ 100 ppl p= .96 95% CI = -24-20% NNT= 500	**6-Year Rate** **RRR= 1% (3% calculated)** ARR= 0.4 events/ 100 ppl p= .88 95% CI = -11-11% NNT= 250	**6-Year Rate** **Heart failure (hospitalized or fatal)** RRR= 1% (3% calculated) ARR= 0.2 events/ 100 ppl p= .89 95% CI = -18-17% NNT= 500
Asselbergs et al 2004 Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT)	1.8% vs 3.5% (NS)	Not reported	0.9% vs 0.9% (NS)	Not reported	Not reported
Colhoun 2004 Collaborative Atorvastatin Diabetes Study (CARDS)	**Any acute cardiovascular disease event:** 9.4% atorva vs 13.4% placebo. Hazard ratio=0.68 (95% CI 0.55, 0.85)	Not reported	Not reported	4.3% atorva vs 5.8% placebo. Hazard ratio=0.73 (95% CI 0.52, 1.01)	**Primary endpoint (acute coronary event, coronary revascularization, stroke):** 5.8% atorva vs 9.0% placebo. Hazard ratio=0.63 (95% CI 0.48, 0.83) **Acute coronary events:** 3.6% atorva vs 5.5% placebo. Hazard ratio=0.64 (95% CI 0.45, 0.91)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Studies in ol			
ALLHAT Officers and Coordinators 2002 Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)	**6-Year Rate** **Fatal & nonfatal** RRR= 9% ARR= 0.5 events/ 100 ppl p= .31 95% CI = -9-25% NNT= 200	NR	
Asselbergs et al 2004 Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT)	1.6% vs 0.9% (NS)	Not reported	
Colhoun 2004 Collaborative Atorvastatin Diabetes Study (CARDS)	1.5% atorva vs 2.8% placebo. Hazard ratio=0.52 (95% CI 0.31, 0.89)	1.7% atorva vs 2.4% placebo. Hazard ratio=0.69 (95% CI 0.41, 1.16)	

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
Downs JR, etal. 1998 Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)	Randomized, double-blind, placebo-controlled, intention to treat analysis	6605 healthy men (43-73 yrs) & postmenopausal women (55-73 yrs) without CHD with average TC, LDL-c and below average HDL-c	Lovastatin 20 mg qpm or placebo qpm. Lovastatin increased to 40 mg qpm if LDL-c >110 mg/dl (2.84 mmol/l).	5.2 years	150 ±17 mg/dl (3.88 mmol/l)	25% (at 1 year)
Heart Protection Study Collaborative Group 2002, 2004 Heart Protection Study (HPS)	Randomized, double-blind, placebo-controlled, intention to treat analysis	20,536 Men or women 40-80 years with a total cholesterol of >135 mg/dl and a substantial 5 year risk for death from coronary heart disease based on their past medical history.	Simvastatin 40 mg qd or placebo qd.	5 years	131 mg/dl (3.4 mmol/L)	29.5% (calculated)
Holdaas et al. 2003 (ALERT)	Randomized, double-blind, intention-to-treat analysis for all randomized	2100 patients of renal or renal/pancreas transplant 6+ months prior w/ stable graft function, total serum cholesterol 4.0-9.0 mmol/L (calculated 154-347 mg/dl). Exclude those using a statin, with familial hypercholesterolemia, life expectancy <1 year, and acute rejection episode in previous 3 months.	Fluvastatin 40 mg daily vs. placebo; dose doubled after 2+ years.	5.1 years	4.1 mmol/L (calculated 158 mg/dl)	32% in 5.1 years mean follow-up

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death	All Cause Mortality	Major Coronary Events
Downs JR, etal. 1998 Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)	**Fatal or nonfatal MI:** RRR=40% ARR=1.2 events/100 ppl p=0.002 95% CI 17-57% NNT=86	**Unstable angina:** RRR=32% ARR=0.8 events/100 ppl p=0.02 95% CI 5-51% NNT=122	There were not enough fatal cardiovascular or CHD events to perform survival analysis.	80 in lovastatin vs. 77 placebo (NS)	**Primary endpoint: First acute major event (fatal or nonfatal MI, unstable angina, or sudden cardiac death** RRR=37% ARR=2 events/100 ppl p<0.001 5% CI 21-50% NNT=49
Heart Protection Study Collaborative Group 2002, 2004 Heart Protection Study (HPS)	**Nonfatal MI:** RRR=38% ARR=2.1/100 ppl pp<0.0001 95% CI 30-46, NNT=47	**Admission for unstable or worsening angina:** RRR=14% ARR=3.5/200 ppl p=0.0003 95% CI not given NNT=28	**Admission for unstable or worsening angina:** RRR=14% ARR=3.5/100 ppl p=0.0003, 95% CI not given, NNT=28	**Primary endpoint:** RRR=13%, ARR=1.75/100 ppl, p=0.0003, 95% CI 6-19%, NNT=57	**Death due to CHD or nonfatal MI:** RRR=27% ARR=3.1/100 ppl p<0.0001, 95% CI 21-33% NNT=32
Holdaas et al. 2003 (ALERT)	Total events RRR = 17%, p=.139 NS Definite nonfatal MI RRR= 32%, p= .05 ARR= 1.9 events/100 ppl 95% CI= 0-60% NNT= 47		**Cardiac death** RRR= 38%, p= .031 ARR= 1.7 events/100 ppl 95% CI= 4-60% NTT= 41		

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Downs JR, etal. 1998 Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)	Not reported	RRR=33% ARR=1.5 events/100 ppl p=0.001 95% CI 15-48% NNT=65	Lovastatin reduced the incidence of first acute major coronary events, MI, unstable angina, coronary revascularization procedures, coronary and cardiovascular events compared to placebo.
Heart Protection Study Collaborative Group 2002, 2004 Heart Protection Study (HPS)	RRR=25%, ARR=1.37/100 ppl, p<0.0001, 95% CI 15-34, NNT=72 (Ischemic stroke accounted for this difference).	RRR=24% ARR=2.6/100 ppl p<0.0001 95% CI 17-30 NNT=38	Coronary or vascular death, nonfatal MI, stroke and need for coronary revascularization reduced for simvastatin group compared to placebo in patients at high risk for CV death. Subanalysis of patients at LDL-c levels <100 mg/dl showed a reduction of to 65 mg/dl (mean) produced a reduction in risk about as great as those at higher LDL-c. CV events were reduced in the simvastatin vs. placebo groups regardless of prerandomization LDL-c lowering response. Simvastatin reduced incidence of the primary endpoint of total mortality, with a CHD death reduction of 42% vs. placebo. Simvastatin reduced incidence of major coronary events. The risk for these events was reduced in women and in those over 60 years.
Holdaas et al. 2003 (ALERT)		CABG or PCI RRR= 11%, p= NS	Rate of total adverse events similar for fluvastatin 40 mg, 80 mg, and placebo groups. Over study period, 14% of placebo group admitted to other lipid-lowering treatments, mostly statins, along with 7% of fluvastatin group. Other concurrent medications similar in both groups: ciclosporin (all), steroids (81%), beta blockers and calcium antagonists (95%), and aspirin (34%)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
Pederson TR et al. 2005 Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL)	Randomized, open-label with blinded end-point classification, multicenter	8888 men and women aged 80 or younger with a history of a definite MI who qualified for statin therapy according to national guidelines at the time of recruitment.	Simvastatin 20 mg or atorvastatin 80 mg . Dose of simvastatin could be increased I to 40 mg if, at 24 weeks, TC was higher than 190 mg/dL. The dose of atorvastatin could be decreased to 40 mg for adverse events.	Median 4.8 years	122±0.5 mg/dL	33% simvastatin, 49% atorvastatin at 12 weeks
Riegger G. et al.. 1998	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	365 men or women 40-70 years with stable symptomatic CHD as assessed by exercise ECG and an LDL-c >160 mg/dl (4.1 mmol/L)	Fluvastatin 40 mg qpm or placebo qpm. If LDL-c was not reduced 30% or more, fluvastatin was increased to 40 mg bidl	1 year	198 mg/dl (5.1 mmol/L)	26.90%
Sacks FM., et al. 1996 Cholesterol and Recurrent Events Trial (CARE)	Randomized, double-blind, placebo-controlled, intention to treat analysis	4159 men and postmenopausal women 21-75 years with an acute MI 3-20 months prior to randomization	Pravastatin 40 mg qpm or placebo qpm.	5 years (median)	139 mg/dl (3.4 mmol/l)	32% (28% vs. placebo)
Scandinavian Simvastatin Survival Study Group 1994 Scandinavian Simvastatin Survival Study (4S)	Randomized, double-blind, placebo-controlled, intention to treat analysis	4444 men and women 35-70 years with a history of angina pectoris or acute MI	Simvastatin 20 mg qpm or placebo qpm	5.4 years (median)	187 mg/dl (4.87 mmol/l)	35%

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death	All Cause Mortality	Major Coronary Events
Pederson TR et al. 2005 Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL)	**Nonfatal MI:** 7.2% simva vs 6.0% atorva (p=0.02) Hazard ratio=0.83 (0.71, 0.98)	**Hospitalization for unstable angina:** 5.3% simva vs 4.4% atorva (p=0.06) Hazard ratio=0.83 (0.69, 1.01)	**CHD death:** 4.0% simva vs 3.9% atorva (p=0.90) Hazard ratio=0.99 (0.80, 1.22) **Cardiovascular death:** 4.9% simva vs 5.0% atorva (p=0.78) Hazard ratio=1.03 (0.85, 1.24)	**All-cause mortality:** 8.4% simva vs 8.2% atorva (p=0.81) Hazard ratio=0.98 (0.85, 1.13)	**Primary endpoint (CHD death, nonfatal MI, cardiac arrest with resuscitation):** 10.4% simva vs 9.3% atorva (p=0.07) Hazard ratio=0.89 (0.78, 1.01)
Riegger G. et al.. 1998	3 cardiac events occurred in the fluvastatin vs. 10 in the placebo group (p<0.05, ARR=4/100 persons, NNT=25).				
Sacks FM., et al. 1996 Cholesterol and Recurrent Events Trial (CARE)	**Fatal or nonfatal MI:** RRR=25% ARR=2.4/100 ppl p=0.006 95% CI 8-39% NNT=41	Not reported	**Death due to CHD:** RRR=20% ARR=1.1/100 ppl p=0.1 95% CI (-)5-39% NNT=89	RRR=9% ARR=0.7/100 ppl p=0.37 95% CI (-)12-26% NNT=128	**Primary endpoint: *Death from CHD or nonfatal MI:*** RRR=24% ARR=3 p=0.003 95% CI 9-36% NNT=33
Scandinavian Simvastatin Survival Study Group 1994 Scandinavian Simvastatin Survival Study (4S)	Not reported separately	Not reported	**Death due to CHD:** RRR=42% ARR=3.5/100 ppl 95% CI 27-54% NNT=28	**Primary endpoint: Total mortality:** RRR=30% ARR=3.3/100 ppl p=0.0003 95% CI 15-42% NNT=30	**CHD Death, nonfatal MI, resuscitated cardiac arrest:** RRR=34% ARR=8.5/100 ppl p<0.00001 95% CI 25-41% NNT=12

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Pederson TR et al. 2005 Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL)	**Fatal or nonfatal stroke:** 3.9% simva vs 3.4% atorva (p=0.20) Hazard ratio=0.87 (0.70, 1.08)	16.7% simva vs 13.0% atorva (p<0.001) Hazard ratio=0.77 (0.69, 0.86)	
Riegger G. et al.. 1998			Fluvastatin resulted in a significant reduction in cardiac events compared to placebo in patients with CHD and elevated LDL-c. Just over 20% of patients withdrew because of noncompliance or lack of cooperation with similar distribution in each group. Fair in quality for assessment of differences in clinical events between groups.
Sacks FM., et al. 1996 Cholesterol and Recurrent Events Trial (CARE)	RRR=31%, ARR=1.1/100 ppl, p=0.03, 95% CI 3-52, NNT=86	RRR=27% ARR=4.7/100 ppl p<0.001 95% CI 15-37% NNT=41	Pravastatin reduced the incidence of the combined primary endpoint of nonfatal MI and death due to CHD. Stroke and need for revascularization was also reduced in the pravastatin compared to placebo group. Overall mortality and mortality from noncardiovascular causes was not reduced. The reduction in coronary events was greater in women and those with higher baseline LDL-c.
Scandinavian Simvastatin Survival Study Group 1994 Scandinavian Simvastatin Survival Study (4S)	**Post-hoc analysis: fatal and nonfatal cerebrovascular events:** RRR=30% ARR=1.2/100 ppl p=0.024 95% CI 4-48% NNT=80	RRR=37% ARR=5.9/100 ppl p<0.00001 95% CI 26-46% NNT=17	Simvastatin reduced the incidence of the primary endpoint of total mortality of which CHD death accounted for a reduction of 42% vs. placebo. Simvastatin also reduced the incidence of major coronary events, as defined in this trial, need for revascularization and combined fatal and nonfatal stroke. The risk for these events was reduced in women and in those over 60 years.

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
Sever 2003 Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA) UK, Sweden, Norway, Denmark, Finland, Ireland	Randomized, double-blind (inadequate information), placebo-controlled, intention-to treat analysis	10,305 people with no history of CHD, total cholesterol concentration ≤ 6.5 mmol/L (calculated = 253 mg/dL), age 40-79, with untreated hypertension or treated hypertension with systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or both; plus 3+ CV risk factors, including male sex, age 55+, and family history.	Atorvastatin 10 mg/day or placebo	3.3 years (median)	3.4 mmol/L (calculated = 133 mg/dL)	**6 months** - base = 35.8% - placebo = 35.9% **Year 2** - base = 34.9% - placebo = 33.5% **Year 3** - base = 33.7% - placebo = 30.9%
Shepherd J., et al. 1995 West of Scotland Coronary Prevention Study Group (WOSCOPS)	Randomized, double-blind, placebo-controlled, intention to treat analysis	6595 Scottish men (45-64 years) with no history of MI and elevated cholesterol	Pravastatin 40 mg qpm or placebo qpm.	4.9 years	192 ± 17 mg/dl (5 mmol/l)	26% in the on-treatment group, 16% in the intent to treat population
Shepherd 2002, 1999 Prospective Study of Pravastatin in the Elderly (PROSPER) Scotland, Ireland, The Netherlands	Randomized, double-blind, placebo controlled, intention-to treat analysis	5804 men and women age 70-82 with pre-existing vascular disease or raised risk due to smoking, hypertension or diabetes.; cholesterol 155-350 mg/dl, triglycerides ≤530 mmol/L and good cognitive function.	Pravastatin 40 mg/day or placebo	3.2 years	3.8 mmol/L (calculated = 148.2 mg/dL)	34% from baseline and placebo at 3 months (2.5 /3.8 mmol/L).

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death	All Cause Mortality	Major Coronary Events
Sever 2003 Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA) UK, Sweden, Norway, Denmark, Finland, Ireland	**Primary endpoint: Nonfatal MI plus fatal CHD** RRR= 36% ARR= 1.1 events/ 100 ppl p= .0005 95% CI = 17-50% NNT= 91	**Unstable angina** RRR= 13% ARR= 0.1 events/ 100 ppl p= .6447 95% CI = -57-51% NNT= 1000	**CV mortality** RRR= 10% ARR= 0.2 events/ 100 ppl p= .5066 95% CI = -23-34% NNT= 500	RRR= 13% ARR= 0.5 events/ 100 ppl p= .1649 95% CI = -6-29% NNT= 200	**Total coronary events** RRR= 29% ARR= 1.4 events/ 100 ppl p= .0005 95% CI =14-41% NNT= 96
Shepherd J., et al. 1995 West of Scotland Coronary Prevention Study Group (WOSCOPS)	**Nonfatal MI:** RRR=31% ARR=1.9 95% CI 15-45% NNT=54	Not reported	**Death from all cardiovascular causes:** RRR=32% ARR 0.7/100 ppl p=0.033 95% CI 3-53% NNT=142	RRR=22% ARR 0.9/100 ppl p=0.051 95% CI 0-40 NNT=112	**Primary endpoint: nonfatal MI or death:** RRR=31% ARR=2.2/100 ppl p<0.001 95% CI 17-43% NNT=44
Shepherd 2002, 1999 Prospective Study of Pravastatin in the Elderly (PROSPER) Scotland, Ireland, The Netherlands	**Nonfatal MI** RRR= 14% ARR=1 events/100 ppl p= .10 95% CI = -3-28% NNT=100	NR	**CHD Death** RRR= 24% ARR= 0.9 events/ 100 ppl p= .043 95% CI = 1-42% NNT= 111	RRR= 3% ARR= 0.2 events/ 100 ppl p= 0.74 95% CI = -14-17% NNT= 500	**All cardiovascular events** RRR= 15% ARR= 2.3events/100 ppl p= .012 95% CI = 3-25% NNT= 43 **Transient ischemic attacks** RRR= 25% ARR= 0.8 events/ 100 ppl p=0.051 95% CI = 0-45% NNT= 125

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Sever 2003 Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA) UK, Sweden, Norway, Denmark, Finland, Ireland	**Fatal & nonfatal** RRR= 27% ARR= 0.7 events/ 100 ppl p= .0236 95% CI = 4-44% NNT= 142	**Total CV events & procedures** RRR= 21% ARR= 2.0 events/ 100 ppl p= .0005 95% CI =10-31% NNT= 50	
Shepherd J., et al. 1995 West of Scotland Coronary Prevention Study Group (WOSCOPS)	46 in pravastatin vs. 51 in placebo (NS)	RRR=37% ARR=0.9/100 ppl p=0.009 95% CI 11-56% NNT=112	Pravastatin reduced the incidence of coronary events (nonfatal MI and CHD death), death from all CHD and cardiovascular causes, need for revascularization and nonfatal MI compared to placebo. There was a trend to reduced all-cause mortality in pravastatin vs. placebo.
Shepherd 2002, 1999 Prospective Study of Pravastatin in the Elderly (PROSPER) Scotland, Ireland, The Netherlands	**Fatal stroke** RRR= -57% ARR= -0.3 events/ 100 ppl p= .19 95% CI = -208-20% NNT= -333 **Nonfatal stroke** RRR= 2% ARR= 0.1 event/ 100 ppl p= 0.85 95% CI = -26-24% NNT= 1000	RRR= 18% ARR= 0.3 events/ 100 ppl p= .36 95% CI = -26-46% NNT= 333	Subgroup analysis shows greater statin effect reducing CHD death and nonfatal MI in men than in women, and in secondary prevention than in primary prevention.

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
Stone PH et al., 2005 The Vascular Basis for the Treatment of Myocardial Ischemia Study	Randomized, double-blind, multicenter	199 (excluding atorvastatin plus vitamins C and E arm) men and women age <85 years, with fasting TC 180 to 250 mg/dL, objective evidence of coronary disease, exercise-induced ST-segment depression >=1.0 mm, and >=1 episode of reversible ST depressiion of >=1.0 mm during 48-hour ambulatory ECG monitoring of routine activities.	Atorva titrated to achieve an LDL of <80 mg/dL or a maximum dose of 80 mg, or control group of diet plus low dose lovastatin, if necessary, to achieve an LDL of <130 mg/dL. 91% of control patients required lovastatin (median dose 5 mg). (Also included an intensive atorva plus vitamins C and E arm)	12 months	atorva: 149±33 control (lova): 151±27	42.9% atorva vs 18.5% control (lova)
The Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group 1998 Colquhoun, 2004 Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	Randomized, double-blind, placebo-controlled, intention to treat analysis	9014 men & women 31-75 years with a history of either MI or hospitalization for unstable angina.	Pravastatin 40 mg qpm or placebo qpm.	6.1 years	150 mg/dl 3.88 (mmol/l) (median)	25% vs. placebo

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death	All Cause Mortality	Major Coronary Events
Stone PH et al., 2005 The Vascular Basis for the Treatment of Myocardial Ischemia Study	1% atorva vs 0% control (p=0.32)	**Unstable angina:** 2% atorva vs 2% control (p=0.54)	Not reported	1% atorva vs 0% control (p=0.32)	**Combined death, MI, unstable angina, stroke, revascularizaton):** 3% atorva vs 1% control (p=0.62)
The Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group 1998 Colquhoun, 2004 Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	**Fatal or nonfatal MI:** RRR=29% ARR=2.8/100 ppl p<0.001 95% CI 18-38% NNT=36	**Unstable angina:** RRR=12% ARR=2.2/100 ppl 95% CI 4-19% NNT=45	**Primary endpoint: Death due to CHD:** RRR=24% ARR=1.9/100 ppl p<0.001 95% CI 12-35% NNT=52	RRR=22% ARR 3/100 ppl p<0.001 95% CI 13-31 NNT=33	**Death due to CHD or nonfatal MI:** RRR=24% ARR=3.5/100 ppl p<0.001) 95% CI 15-32% NNT=28

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Stone PH et al., 2005 The Vascular Basis for the Treatment of Myocardial Ischemia Study	1% atorva vs 1% control (p=0.77)	3% atorva vs 1% control (p=0.41)	Primary outcome was ischemia by ambulatory ECG
The Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group 1998 Colquhoun, 2004 Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)	RRR=19% ARR=0.8/100 ppl p=0.48 95% CI 0-34% NNT=127	RRR=20% ARR=3/100 ppl p<0.001 95% CI 10-28% NNT=34	Pravastatin reduced the incidence of death from CHD, overall mortality, fatal and nonfatal MI and need for revascularization compared to placebo.

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
Wanner C et al., 2005 4D Study	Randomized, double-blind, multicenter	1255 men and women with type 2 diabetes, ages 18 to 80 years, who had been receiving maintenance hemodialysis for less than 2 years.	Atorva 20 mg or placebo. If LDL-C levels fell below 50 mg/dL, the dose of atorva ws reduced to 10 mg.	Median 4 years	126 ± 30 mg/dL	42.0% atorva vs 1.3% placebo

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death	All Cause Mortality	Major Coronary Events
Wanner C et al., 2005 4D Study	**Nonfatal MI:** 11% atorva vs 12% placebo (p=0.08) Relative risk=0.81 (0.64, 1.03) **Fatal MI:** 4% atorva vs 5% placebo (p NR)	Not reported	**Death from cardiac causes:** 20% atorva vs 23% placebo (p=0.42) Relative risk=0.88 (0.64, 1.21)	48% atorva vs 50% placebo (p=0.33) Relative risk=0.93 (0.79, 1.08)	**All cardiac events combined (death from cardiac causes, nonfatal MI, PTCA, CABG, other interventions to treat coronary heart disease):** 33% atorva vs 39% placebo (p=0.03) Relative risk=0.82 (0.68, 0.99)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Wanner C et al., 2005 4D Study	**Stroke:** 10% atorva vs 7% placebo (p=0.15) Relative risk=1.33 (0.90, 1.97) **TIAA or prolonged reersible ischemic neurologic deficit:** 4% atorva vs 5% placebo **All cerebrovascular events combined:** 13% atorva vs 11% placebo (p=0.49) Relative risk=1.12 (0.81, 1.55)	**PTCA:** 7% atorva vs 7% placebo **CABG:** 4% atorva vs 5% placebo	

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
Studies in inpatients with unstable angina or acute coronary syndrome						
Arntz et.al 2000 L-CAD	Randomized, double-blind, vs standard care, intention-to-treat	126 men and women with total cholesterol >200 to <400 mg/dl and LDL cholesterol >130 to <300 mg/dl with an acute MI and/or who underwent emergency PTCA due to severe or unstable angina pectoris.	pravastatin 20 to 40 mg vs usual care; started on average 6 days after MI or PTCA	2 years	prava vs usual care 176 mg/dL (131-240) vs 172 mg/dL (132-239)	prava vs usual care 28% vs no change
Cannon et al 2004 PROVE-IT	Randomized, head-to-head, double-blind	4162 men and women age 18 or older who had been hospitalized for an acute coronary syndrome (MI or high-risk angina) in the preceding 10 days, but stable. Total cholesterol level 240 mg/dL or less. If receiving long-term lipid-lowering therapy, total cholesterol level 200 mg/dL or less.	pravastatin 40 mg vs atorvastatin 80 mg.	2 years (range 18 to 36 months)	Median (interquartile range): prava 106 (87-127) mg/dL; atorva 106 (89-128) mg/dL	2985 patients who had not previously received statin therapy: 22% prava vs 51% atorva at 30 days (p<0.001)
de Lemos 2004 A to Z Trial (Phase Z)	Randomized, double-blind, placebo-controlled, multicenter	4497 men and women ages 21-80 with either non-ST-elevation acute coronary syndrome or ST elevation MI with a total cholesterol level of 250 mg or lower.	Early intensive statin treatment (simvastatin 40 mg for 30 days and then simvastatin 80 mg there after) vs less aggressive strategy (placebo for 4 months and then simvastatin 20 mg thereafter)	Median 721 days (range 6 months to 24 months)	Median 112 (25th-75th percentiles 94-131)	simvastatin first vs placebo first 1 month: 39% vs +10% (p<0.001) 4 months: 45% vs +12% (p<0.001) 8 months: 44% vs 31% (p<0.001) 24 months: 41% vs 27% (p<0.001)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death	All Cause Mortality	Major Coronary Events
Studies in inpatient					
Arntz et.al 2000 L-CAD	1 in usual care group.			2 deaths in each group.	1 ischemic stroke in each group
Cannon et al 2004 PROVE-IT	death or MI: 18% reduction (p=0.06)	recurrent unstable angina: 29% reduction in atorva group (p=0.02)	prava vs atorva 22.3% vs 19.7% (p=0.029)	28% reduction in atorva group (p=0.07)	infrequent, but rates did not differ significantly between groups
de Lemos 2004 A to Z Trial (Phase Z)	Hazard ratio 0.96 (95% CI 0.61, 1.02)	Not reported	Hazard ratio 0.75 (95% CI 0.57, 1.00)	Hazard ratio 0.79 (0.61, 1.02)	**Primary end point (cardiovascular death, myocardial infarction, readmission for acute coronary syndrome, or stroke):** Hazard ratio 0.89 (95% CI 0.76, 1.04; p=0.14)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Studies in inpatient			
Arntz et.al 2000 L-CAD	11/70 prava vs 24/56 usual care (15.7% vs 42.9%)		
Cannon et al 2004 PROVE-IT	14% reduction in atorva group (p=0.04)		
de Lemos 2004 A to Z Trial (Phase Z)	Hazard ratio 0.79 (95% CI 0.48, 1.30)	Hazard ratio 0.93 (95% CI 0.73, 1.20)	

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline
Den Hartog et al. 2001 (Pilot Study)	Pilot study; randomized, double-blind, placebo controlled.	99 men and women with acute MI or unstable angina who were hospitalized for less than 48 hours.	pravastatin 40 mg	3 months	4.51 mmol/dL	25%
Liem et al 2002 FLORIDA	Randomized, double-blind, placebo-controlled,	540 men and women with an MI and total cholesterol taken at admission or within 24 hours after onset of symptoms was 6.5mmol/L or higher; eligibility also required one of the following: new or markedly increased chest pain lasting longer than 30 minutes, or a new pathological Q wave.	fluvastatin 80 mg	1 year	135 mg/dl vs 139 mg/dl	fluva vs placebo: 21% decrease vs 9% increase
Schwartz et al. 2001 MIRACL	Randomized, double-blind, placebo-controlled	Men and women age 18 or older with unstable anginal or non-Q-wave MI.	atorvastatin 80 mg	16 weeks	124 mg/dL	atorva vs placebo: 40% decrease vs 12% increase (adjusted mean)
Thompson et al 2004 PACT	Randomized, double-blind, placebo-controlled, multicenter	3408 men and women age 18 to 85 within 24 hours of onset of acute MI or unstable angina.	pravastatin 40 mg (20 mg for those subjects enrolled in the early stages of the study) for 4 weeks.	4 weeks	Not reported. Mean total cholesterol 219	Not reported

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death	All Cause Mortality	Major Coronary Events
Den Hartog et al. 2001 (Pilot Study)	2/50 vs 1/49 (NS)	24/50 vs 21/49 (NS)	2/50 vs 2/49		
Liem et al 2002 FLORIDA				2.6% vs 4.0% (p not reported, NS?)	
Schwartz et al. 2001 MIRACL	No significant differences			No significant differences	
Thompson et al 2004 PACT	nonfatal only: 0.8% vs 0.9% (NS) fatal and nonfatal: 3.8% vs 3.7% (NS)	new unstable angina: 2.4% vs 2.2% (NS) recurrent unstable angina: 4.7% vs 5.2% (NS)	Fatal MI: 0.8% vs 0.9% (NS) Death excluding fatal MI: 0.6% vs 1.3% (NS)	1.4% vs 2.2% (NS)	11.6% vs 12.4% (NS)

Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Stroke	Need for Revascularization (CABG, PTCA, Stenting)	Comments/Conclusions
Den Hartog et al. 2001 (Pilot Study)	11/50 vs 9/49 (NS)		
Liem et al 2002 FLORIDA			
Schwartz et al. 2001 MIRACL			
Thompson et al 2004 PACT	NR	NR	

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
Studies from Evidence Table 1							
Andrews 2001	Yes	Not reported	Yes	Yes	No	No	No
Assman 1999	Yes	Not reported	Yes	Yes	No details given	No details given	No details given
Bays 2005	Method not reported	Not reported	Yes	Yes	No- open label	No- open label	No- open label
Berger 1996	Method not reported	Not reported	Yes	Yes	No	No	No
Berne 2005	Method not reported	Not reported	Yes	Yes	Yes	Not reported	Described as "double-blind", but no details
Bertolini 1997	Yes	Not reported	Yes, not much detail	Yes	Yes	Yes	Yes
Branchi 2001	Yes	Not reported	Not enough detail given	Yes	Not reported	Not reported	Not reported

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
Studies from Evi					
Andrews 2001	No	Yes	Attrition-yes, crossovers-no, adherence-no, contamination-no	High loss to follow up or drop outs ranging from 14-24% of each group.	Poor-high early withdrawal rate, no reasons noted. LDL-c for Simva not as great as atorva and % meeting LDL-c also lower, possible that doses of simva not titrated
Assman 1999	No	Yes	Attrition: yes, but no details on reasons for withdrawal crossovers-no, adherence-yes, and contamination-no	No	Fair-poor-LDL no details on blinding, Poor-safety no details on dose related adverse effects
Bays 2005	Unable to determine. States used intention to treat, but not defined.	Unable to determine.	No.	Not reported	Fair-Poor
Berger 1996	Yes	Yes	No	Not clear	Fair
Berne 2005	No (465/469 analyzed)	Yes	Attrition yes, others no.	No	Fair
Bertolini 1997	No	Yes	Attrition-reported but no details on reasons for withdrawal. Crossovers-no, adherence to treatment-yes, contamination-no.	No	Fair-LDL lowering Poor-safety (no details on serious adverse effects and dropouts)
Branchi 2001	No	Not enough detail provided-age, etc.	Attrition-yes, crossovers-no, adherence-no, contamination-yes	No	Fair-poor-LDL lowering unsure of blinding, comparable groups, study planned up to 6 months, but high drop out. Poor-safety not enough detail provided.

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
Brown 1998	Yes	Not reported	Yes	Yes	No	No	No
Chan 2004	Study states "blindly randomized," but no details given.	Study states "blindly randomized," but no details given.	Yes	Yes	Study states "blindly randomized," but no details given.	Study states "blindly randomized," but no details given.	Study states "blindly randomized," but no details given.
Dart 1997	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
Davidson 1997	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
Farnier 2000	Yes	Not reported	Yes	Yes	Yes	No	No
Ferdinand 2006	Method not reported	Not reported	Yes	Yes	No- open label	No- open label	No- open label

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
Brown 1998	No	Yes	Attrition-only reported for adverse effects, crossovers-no, adherence-yes-contamination-no	No	Fair-LDL lowering equivalent doses not compared, treat to target. Safety-poor no details on reasons for withdrawal due to adverse effects or doses.
Chan 2004	Not clear	Not reported	Attrition - yes; crossovers - no; adherence - yes; contamination - no.	No (atorv: 5 withdrawals (8.3%) and simva 7 withdrawals (11.7%))	Poor to fair
Dart 1997	No	Yes	Attrition-reported but no details on reasons for withdrawal. Crossovers-no, adherence to treatment-no,	No	Fair-LDL lowering Poor-safety (no details on serious adverse effects, dose and dropouts)
Davidson 1997	Unsure	Yes	Attrition-yes, crossovers-no, adherence-yes, contamination-no	No	Fair-LDL lowering Poor-safety (no details on serious adverse effects and dropouts)
Farnier 2000	Yes	Yes	Attrition reported for adverse effects but no details for other reasons for withdrawal. crossovers-no, adherence-	No	Fair-poor-LDL lowering, open-label, no details on withdrawal. Poor-safety-minimal details provided on adverse effects for each
Ferdinand 2006	No- analyzed patients with at least one dose of study medication and 1 baseline and 1 post-baseline lipid evaluation; used LOCF for dropouts.	Yes	Attitiont yes, others no	No (2% rosuva, 1.3% atorva)	Fair

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
Fonseca 2005	Method not reported	Not reported	Yes	Yes	No- open label	No- open label	No- open label
Gentile 2000	Yes	Not reported	Yes	Yes	No	No	No
Hunninghake 1998	Yes	Not reported	Yes	Yes	No	No	No
Illingworth 2001	Yes	Not reported	More women in the atorva group	Yes	Yes	Yes	Yes
Insull 2001	Yes	Not reported	Yes	Yes	No	No	No
Jacotot 1995	Yes	Not reported	Yes, for height, weight, BMI	Yes	Yes	Yes	Yes

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
Fonseca 2005	No- analyzed patients who had a baseline measurement and received at least one dose of study medication; used LOCF for those who withdrew before 12 weeks. 94.7% of rosuva, 96.6% atorva included in ITT analysis	Unable to determine	Attrition yes, others no	rosuva 8.2%, 4.8% atorva	Fair
Gentile 2000	No	Yes	Attrition-yes, crossovers-no, adherence-no, contamination-yes	No	Fair-poor LDL lowering. Nonequivalent doses compared. Fair-safety
Hunninghake 1998	No	Yes	Attrition-not reported, crossovers-no, adherence-yes, contamination-no	No	Fair-LDL lowering equivalent doses not compared, treat to target. Safety-poor no details on reasons for withdrawal due to adverse effects or doses.
Illingworth 2001	No	More women in the atorva group	Attrition-only reported for adverse effects; Crossovers-no; Adherence-no; Contamination-no	Do not know	Fair-LDL-lowering, Fair-good-safety
Insull 2001	No	Yes	Attrition-no, crossovers-no, adherence-no, contamination-no	Do not know	Poor-equivalent doses not compared. Fair-safety although short-term study.
Jacotot 1995	Yes and on treatment analysis too.	Yes	Attrition-yes, crossovers-no, adherence-no, contamination-no	No	Fair-LDL lowering. Fair-safety although no doses provided at which adverse effects occurred.

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
Jones 1998	Yes	Not reported	Yes-not much detail. LDL-c slightly lower for 3 of 4 atorva groups.	Yes	No	No	No
Jukema 2005	Method not reported	Not reported	Yes	Yes	No-open label	No- open lable	No- open label
Karalis 2002	Method not reported	Not reported	some differences- more men in atorva 10mg than simva 20mg, and BP higher in simva vs atorva group	Yes	Yes	Not reported	No
Marz 1999	Yes	Not reported	Yes	Yes	Yes-serious adverse effects	No	No
Nash 1996	Yes	Not reported	No-higher rate of musculo-skeletal conditions in lova group.	Yes	No	No	No
Olsson 2003	Method not reported	Not reported	Yes	Yes	Yes	Yes	Yes
Ose 1995	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
Paragh 2004	Yes, though method not reported	Not reported	Not reported	Yes	No - open label	Not reported - open label	No - open label

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
Jones 1998	No	Yes, but LDL-c lower for 3 of 4 atorva groups	Attrition-yes, crossovers-no, adherence-no, contamination-no	No	Fair-poor LDL lowering. Small sample size in certain groups and LDL-c was lower for 3 out of 4 atorva groups. Fair-poor-safety. Eight patients lost to follow up.
Jukema 2005	Yes (used LOCF)	Yes	Attrition yes, others no.	No	Fair
Karalis 2002	No	Not enough detail provided	No	Not reported	Poor- differences at baseline, randomization and allocation methods not reported, not ITT, withdrawals not clear.
Marz 1999	Do not know	Yes	Attrition-reported, crossovers-no, adherence-no, contamination-no	No	Fair-LDL-lowering, Fair-safety although no details on dose at which adverse effects occurred
Nash 1996	Yes	No-higher musculoskeletal conditions in lova.	Attrition-yes, crossovers-no, adherence-yes, contamination-no	No	Fair-LDL lowering. Poor-safety since higher rate of musculo-skeletal conditions in lova group. Also no doses at which adverse effects in fluva group occurred.
Olsson 2003	No	Yes	Attrition and adherence yes, others no	No	Fair
Ose 1995	No	Yes	Attrition-yes, crossovers-no, adherence-yes, contamination-no	No	Fair-LDL lowering. Fair-safety.
Paragh 2004	Not clear	N/A - it was a crossover study.	Attrition - no; crossovers - no; adherence - no; contamination - no	Not reported	Poor to fair. Poor - safety. No specific details about adverse events or withdrawals given.

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
Recto 2000	Yes	Not reported	Yes	Yes	No	No	No
Saklamaz 2005	Method not reported	Not reported	Yes	Yes	Not reported	Not reported	Not reported
Schaefer 2003	Method not reported	Not reported - open label	Yes	Yes	No - open label	Not reported - open label	No - open label
Schulte 1996	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
Schuster 2004	Yes	Not reported	Yes	Yes	No - open label	Not reported - open label	No - open label
Schwartz 2004	Yes	Not reported	Yes	Yes	Yes	Not reported	Yes
Sigurdsson 1998	Method not reported	Not reported	Simva group slightly older (61.4 years vs 59.3 years, p=0.059)	Yes	Yes	Not reported	Yes
Stalenhoef	Method not reported	Not reported	Yes	Yes	Yes	Not reported	Described as "double-blind", but no details

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
Recto 2000	No	Yes	Attrition-yes, crossovers-yes, adherence-not reported, contamination-N/A	No	Fair-LDL lowering. Fair-safety included details on withdrawal and adverse effects.
Saklamaz 2005	Yes	Yes	No	No loss to followup	Fair
Schaefer 2003	Yes	Not reported	Attrition - no; crossovers - no; adherence - no; contamination - no.	Not reported	Fair/poor-LDL lowering: No drop-out data nor loss to follow-up data given. Poor - safety: no data given on any adverse effects nor on withdrawals due to adverse effects.
Schulte 1996	Unable to determine	Yes	Attrition-no, crossovers-no, adherence-yes, contamination-no	Unable to determine the number completing study	Fair-poor-LDL lowering: Drop outs and loss to follow up not given. Fair-poor safety:not sure how many actually dropped out due to adverse effects (22)
Schuster 2004	Yes	Not reported	Attrition -yes; crossovers - no; adherence - yes; contamination - no.	No	Fair
Schwartz 2004	Yes	Not reported	Attrition -yes; crossovers - yes; adherence - no; contamination - no.	No	Fair - This study was designed to look at paraoxonase activity. Poor - safety. No specific details about adverse events or withdrawals given.
Sigurdsson 1998	Yes	Yes	Attrition yes, others no.	No	Fair
Stalenhoef	No (397/401 analyzed)	Yes	Attrition yes, others no	No	Fair

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
Strandberg 2004	Yes	Not reported	Yes	Yes	No - open label	Not reported - open label	No - open label
Van Dam 2000	Yes-computer lists (adequate)	Not reported	No-patient risk factors Yes-lipoprotein levels	Yes	Yes	Yes	No
Wolffenbuttel 1998	Yes	Not reported	N/A cross-over trial	Yes	No	No	No
Wolffenbuttel 2005	Method not reported	Not reported	Yes	Yes	No- open label	No- open label	No- open label

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
Strandberg 2004	Yes	Not reported	Attrition - yes; crossovers - no; adherence - no; contamination - no.	No.	Fair
Van Dam 2000	No	Were not the same to start with for risk factors. Lipoprotein levels-yes	Attrition-no reasons for withdrawal given. Crossovers-no, adherence to treatment-yes, contamination-no	No	Fair-poor-LDL single-blinded, not intent to treat, 14% loss to follow up, Poor-safety no details on dose related adverse effects or withdrawals.
Wolffenbuttel 1998	No	N/A-cross-over	Attrition-yes, crossovers-yes, adherence-no, contamination-no	No	Fair-LDL lowering, Fair-poor safety. Short-term trial using relatively low statin doses.
Wolffenbuttel 2005	Yes (used LOCF)	Yes	Attrition due to AEs only reported.	No	Fair

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
Studies from Evidence Table 2							
A to Z de Lemos 2004	Yes	Yes	More simvastatin patients had prior MI (18% vs 16%, p=0.05), otherwise similar	Yes	Yes	No details given	Yes
AFCAPS 1998	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
ALLHAT-LLC *(open trial)*	Adequate; computer-generated scheme	adequate; centralized	Yes	Yes	No	No	No
Arntz et al 2000 L-CAD	Method not reported	Not reported	Yes	Yes	Yes	Yes	Yes
ASCOT	NR	NR	Yes	Yes	Yes	Yes	Yes
Cannon et al 2004 PROVE-IT	Method not reported	Not reported	History of peripheral arterial disease more common in prava group, uneven treatment group sizes.	Yes	Yes	Not reported	Yes
CARDS Colhoun 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
Studies from Evi					
A to Z de Lemos 2004	Yes	Yes	Attrition yes,	No	Fair
AFCAPS 1998	Yes	Yes	Attrition-yes, crossovers-no actual numbers provided, adherence-yes and contamination-no actual numbers provided.	No	Good
ALLHAT-LLC *(open trial)*	Yes	NR	Attrition unclear; Crossover(years 2/4/6): 8.2%/17.1%/26.1%; Adherence(years 2/4/6): 87%/80%/77%; Contamination NR	No	Fair-Good
Arntz et al 2000 L-CAD	Yes- able to calculate		Attrition yes, others no	Yes: 9 patients in control group withdrew consent after learning treatment assignment.	Fair
ASCOT	Yes	NR	Attrition unclear; others NR	No	Fair-Good
Cannon et al 2004 PROVE-IT	Not clear	Yes	Attrition yes, others no	No.	Fair
CARDS Colhoun 2004	4 patients not included, but able to calculate	Yes	attrition, adherence yes, others no.	No	Good

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
CARE 1996	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Den Hartog (Pilot Study)	Yes	Not reported	Some differences	Yes	Yes	Not reported	Yes
4S 1994	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Holdaas	NR	Adequate; serially-numbered identical medication packs	Yes	Yes	Yes	Yes	Yes
HPS	NR	Adequate; centralized	Unclear; "good balance" indicated; data NR	Yes	Yes	Yes	Yes
IDEAL Pederson 2005	NR	NR	Yes	Yes	Yes	No- open label, blinded endpoint classification	No- open label, blinded endpoint classification
Liem et al 2002 FLORIDA	Method not reported	Not reported	Yes	Yes	States "double blind," but no details.	Not reported	States "double blind," but no details.

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
CARE 1996	Yes	Yes	Attrition: yes, crossovers-no, adherence-no, and contamination-yes	No	Good
Den Hartog (Pilot Study)	Yes	No	Attrition yes, others no	No, 2 placebo vs 0 prava lost to followup. High discontinuation rate (22%) and more placebo patients discontinued overall (26.5% vs 16%)	Poor
4S 1994	Yes	Yes	Attrition-yes, crossovers-no, adherence-reported as good with no details provided, and contamination-no.	No	Good
Holdaas	Yes	NR	Attrition=314 (14.9%); others NR	No	Good
HPS	Yes	NR	Attrition=13.9%; Crossovers NR; Adherence (>/= 80%)=82%; Contamination=4002(19.5%) taking non-study statin	No	Good
IDEAL Pederson 2005	Yes	Yes	Attrition and adherence reported.	No	Fair
Liem et al 2002 FLORIDA	Yes	Yes	Attrition and adherence yes, crossover and contamination no	No	Fair

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
LIPID 1998	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
MIRACL Schwartz et al 2001	Method not reported	Not reported	Yes	Yes	Yes	Yes	Yes
PACT Thompson 2004	Method not reported	Not reported	Higher total cholesterol in placebo group, more placebo patients on HRT, and more prava patients on anticoagulants.	Yes	Yes	Yes	Yes
PREVEND IT Asselbergs 2004	Yes	Not reported	Appear similar	Yes	Yes	No details given	Yes
PROSPER	Adequate; computer-generated scheme	Adequate; centralized	Yes	Yes	Yes	Yes	Yes
Stone et al 2005	NR	NR	atorva group higher weight (198 lbs vs 188 lbs control), otherwise similar	Yes	Yes	Not specified	Yes
Wanner et al 2005	Yes	NR	Yes	Yes	Yes	Not specified (but described as double-blind)	Not specified (but described as double-blind)
WOSCOPS 1995	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
LIPID 1998	Yes	Yes	Attrition: yes, crossovers-no, adherence-no, and contamination-yes	No	Good
MIRACL Schwartz et al 2001	Yes	Yes	Attrition yes, others no	No	Fair
PACT Thompson 2004	2.5% lost to followup not included in analysis, but possible to calculate ITT results	Unable to assess	Attrition, adherence yes, others no.	No, 2.5% overall, 45 in each group.	Fair-Poor
PREVEND IT Asselbergs 2004	Yes	Yes	Yes	No	Fair
PROSPER	Yes	NR	Attrition=1449(24.9%); Adherence (average)=94%; others NR	NR	Good
Stone et al 2005	Not clear. 85% completed, numbers and reasons for withdrawal are given.	Unable to determine-numbers withdrawing NR by group.	Attrition and adherence reported.	No	Fair
Wanner et al 2005	Yes	Yes	Attrition and adherence reported.	No	Fair
WOSCOPS 1995	Both intention to treat and on treatment analysis	Yes	Attrition-yes, crossovers-no, adherence-no details and contamination-no	No	Good

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Randomization adequate?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?	Patient unaware of treatment?
Studies from Evidence Table 6: Post-revascularization							
LIPS	NR	Adequate; serially-numbered identical medication packs	No, more fluva patients with diabetes mellitus (14.2% vs 9.8%; p<0.05)	Yes	Yes	Yes	Yes

Evidence Table 3. Internal Validity of Included Trials

Study or Author Year	Intention-to-treat analysis?	Maintained comparable groups?	Reported attrition, crossovers, adherence, and contamination?	Different or overall high loss to follow-up?	Score (good/ fair/ poor)
Studies from Evi ***Post-revascu***					
LIPS	Yes	NR	Attrition= 124(7.4%); others NR	No	Fair

Evidence Table 4. External Validity of Included Trials

Study Year	Similarity of Population to Disease Population	Number recruited
	Studies from Evidence Table 1 (LDL-c lowering)	
Andrews 2001	Men and women 18-80 years with or without CHD and elevated cholesterol	Not reported
Assman 1999	Men and women 18-80 years with elevated cholesterol.	Not reported
Bays 2005	Men and women with elevated LDL-c and low HDL-c; 21% had established CHD; 50% had at least 2 CHD risk factors.	Number screened NR/315 randomized
Berne 2005	Men or women with a history of type 2 diabetes for at least 3 months, being treated with diet, oral antidiabetic medication, insulin, or a combination of these treatments, and fasting LDL-C of >=3.3 mmol/L and triglycerides <6.0 mmol/L at enrollment.	Number screened NR/ 469 randomized

Evidence Table 4. External Validity of Included Trials

Study Year	Exclusion Criteria	Funding Source
Andrews 2001	7,542 patients screened and 3,916 patients randomized to study. Only 3,262 patients completed study. Patients with active liver disease, hepatic impairment, uncontrolled type 1 or 2 DM, or serum creatinine >2 mg/dl.	Study was funded by Pfizer. One employee of Pfizer was acknowledged for their analysis and interpretation of the data.
Assman 1999	Pregnant or breastfeeding women, BMI >32, impaired hepatic function, CK elevation, more than 14 alcoholic drinks per week, s/p MI, PTCA, CABG within the last 3 months or severe or unstable angina, uncontrolled hypertension. No numbers provided for exclusion.	Not reported, although 2 of the authors are employed by Parke-Davis Pharmaceuticals
Bays 2005	Known prior allergy or intolerability to any of the study drugs, H/O substance abuse or dependence within 12 months of screening, consumption of >14 alcoholic drinks per week, uncontrolled psychiatric disease, participation in another investigational study within 30 days of screening, or probucol administration within the previous year. H/O: active gallbladder disease; uncontrolled hypertension; renal insufficiency (serum creatinine ≥1.5 mg/dl); hepatic dysfunction (aspartate aminotransferase or alanine aminotransferase >1.3 times the upper limit of normal); fasting glucose ≥115 mg/dl; New York Heart Association class III/IV congestive heart failure; active gout symptoms or uric acid >1.3 times the upper limit of normal; active peptic ulcer disease; type 1 or 2 diabetes; fibromyalgia; cancer within the previous 5 years (except for basal cell carcinoma); unstable angina, myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or stroke within prior 6 months; or any condition or laboratory abnormality which, in the opinion of the investigator, might be adversely affected by the study procedures or me	Kos Pharmaceuticals
Berne 2005	Type 1 diabetes, uncontrolled type 2 diabetes, uncontrolled hypothyroidism or hypertension, nephrotic syndrome or severe renal failure, active liver disease or hepatic dysfunction active arterial disease serum creatiine kinase levels >3 X ULN, BMI >35, and known hypersensitivity to statins.	AstraZeneca

Evidence Table 4. External Validity of Included Trials

Study Year	Control Group Standard of Care	Length of followup/withdrawals
Andrews 2001	Yes	3916 randomized to study, 3262 completed study. Data from 3757 was analyzed.
Assman 1999	Yes	52 weeks. Withdrawal for adverse effects was reported, but no information on dose or type of AE. No details on number dropping out of the study for other reasons.
Bays 2005	Yes	16 weeks. No information on withdrawals or AEs.
Berne 2005	Yes	12 weeks. 4.7% rosuva vs 5.2% atorva withdrew; 1.3% rosuva vs 3.0% atorva withdrew due to AEs.

Evidence Table 4. External Validity of Included Trials

Study Year	Similarity of Population to Disease Population	Number recruited
Bertolini 1997	Men and women 18-80 years with elevated cholesterol.	Not reported
Branchi 2001	Men or women with elevated cholesterol	Not reported
Brown 1998	Men or women 18-80 years with CHD and elevated LDL-c	Not reported
Chan 2004	120 men and women aged 20-75 years with Type 2 diabetes and with mixed hyperlipidemia (serum trig = 2.3-4.5 mmol/L and LDL-c >= 3.4 mmol/L).	NR/120 randomized
Dart 1997	Men and women 18-80 years with elevated cholesterol.	Not reported
Davidson 1997	Men and women 18-80 years with elevated cholesterol.	Not reported
Farnier 2000	Men or women 18-70 years with elevated LDL-c	Not reported
Ferdinand 2006	African American men and women aged 18 and older who were diagnosed with type IIa or IIb hypercholesterolemia.	2385 screened/ 774 randomized

Evidence Table 4. External Validity of Included Trials

Study Year	Exclusion Criteria	Funding Source
Bertolini 1997	Pregnant or breastfeeding women, uncontrolled hypothyroidism, hypertension, DM, or other endocrine disorder, impaired hepatic or renal function, more than 14 alcoholic drinks per week, taking a drug with the potential for interaction with statins. No numbers provided for exclusion.	Not reported, although 2 of the authors are employed by Parke-Davis Pharmaceuticals
Branchi 2001	200 patients randomized, analysis performed on 199 patients. Patients with hepatic or renal impairment, uncontrolled Type 2 DM, Type 1 DM were excluded. No numbers provided for exclusion at each step.	Not reported
Brown 1998	318 randomized, efficacy analysis performed on 308 patients. Pregnancy or breast-feeding, secondary hyperlipoproteinemia, uncontrolled endocrine disorders, hepatic or renal impairment, MI, CABG, PTCA, unstable angina 1 month prior to screening, participation in another study, uncontrolled type 2 DM, type 1 DM, taking a drug with the potential for interaction with statins. No numbers provided for exclusion at each step.	Funded by Parke-Davis. One author was employed by Parke-Davis
Chan 2004	Not reported	Not reported
Dart 1997	Pregnant or breastfeeding women, uncontrolled hypothyroidism, hypertension, DM, or other endocrine disorder, impaired hepatic or renal function, BMI>32, more than 14 alcoholic drinks per week, taking a drug with the potential for interaction with statins. No numbers provided for exclusion	Study supported by Parke-Davis Pharmaceutical Research as well as listed as a contributor.
Davidson 1997	Impaired hepatic or renal function, Type I DM, uncontrolled DM, any unstable medical condition, noncompliant, enrolled in another trial, taking a drug with a potential for interaction. No numbers provided for exclusion.	Not reported, although Parke-Davis Pharmaceutical is listed as a contributor.
Farnier 2000	331 patients entered prerandomization dietary placebo run-in phase, and 272 were randomized. Pregnant or breastfeeding women, BMI >32, impaired hepatic function, CK elevation, more than 4 alcoholic drinks per day, s/p MI, PTCA, CABG, CVA within the last 3 months, secondary hyperlipidemia, taking a drug with the potential for interaction with statins. No numbers provided for exclusion at each step.	Study financially supported by Parke-Davis and Pfizer.
Ferdinand 2006	History of homozygous familial hypercholesterolemia or known type I, III, or V hyperlipoproteinemia; active arterial disease (e.g., unstable angina, MI, TIA, CVA, CABG or angioplasty within 3 months of trial entry); uncontrolled hypertension; poorly controlled diabetes; active liver disease or dysfunction; unexplained serum creatinekinase levels >3 times ULN, and serum creatinine 2.0 mg/dL.	AstraZeneca

Evidence Table 4. External Validity of Included Trials

Study Year	Control Group Standard of Care	Length of followup/withdrawals
Bertolini 1997	Yes	52 weeks. Withdrawal for adverse effects was reported 19% vs. 26% in the atorvastatin vs. pravastatin group (p>0.05). No details on number dropping out of the study for other reasons.
Branchi 2001	Yes	8-week dietary run-in. 200 patients randomized, 1 lost to follow up
Brown 1998	Yes	Optional 8-week dietary phase, 4-week dietary run-in phase 318 randomized, but 308 included in efficacy analysis.
Chan 2004	Not reported	18 weeks. Withdrawals (atorva n=5 (8.3%) and simva n=7 (11.7%)) reported as due to non-compliance. No data given on specific adverse events or on withdrawals.
Dart 1997	Yes	52 weeks. Withdrawal for adverse effects was reported , but no information on dose or type of AE. No details on number dropping out of the study for other reasons.
Davidson 1997	Yes	52 weeks. At 16 weeks, 16 (12%) from placebo, 50 (7%) from atorvastatin, and 15 (8%) from lovastatin had withdrawn. At 52 weeks, 130 patients had withdrawn. No details on number from each group or reasons for withdrawal were given.
Farnier 2000	Yes	12 weeks. 2 patients withdrew due to AE, no other details given on dropouts.
Ferdinand 2006	Yes	6 weeks. 29 (7.4%) rosuva and 23 (6.0%) atorva patients withdrew. 3.3% of rosuva and 1.3% of atorva patients withdrew due to AEs.

Evidence Table 4. External Validity of Included Trials

Study Year	Similarity of Population to Disease Population	Number recruited
Fonseca 2005	Patients age 18 and older with primary hypercholesterolemia, with fasting LDL-C >5 mg/dL above their NCEP ATP III goal by risk category.	1644 screened/ 1124 randomized
Gentile 2000	Men and women 50-65 years with type 2 DM and elevated cholesterol.	Not reported
Hunninghake 1998	Men or women 18-80 years at risk for CHD and elevated cholesterol.	Not reported
Illingworth 2001	Men or women 21-70 years with an elevated LDL-c	Not reported
Insull 2001	Men or women 18-80 years with elevated LDL-c	Not reported
Jacotot 1995	Men and women 18-75 years with hypercholesterolemia.	Not reported
Jones 1998	Men or women 18-80 years with elevated cholesterol	Not reported

Evidence Table 4. External Validity of Included Trials

Study Year	Exclusion Criteria	Funding Source
Fonseca 2005	Familial hypercholesterolemia, fasting TG levels >400 mg/dL, aspartate aminotransferase or alanine aminotransferase ≥1.5 times ULN, unstable angina, serum creatine kinase >3 times ULN, serum creatinine >2.5 mg/dL, uncontrolled hypertension, uncontrolled diabetes, history of hypersensitivity to other statins, history of alcohol or drug abuse and the use of other hypolipidemic drugs or disallowed medication, such as those with known interactions with statins (e.g., cyclosporine); women of childbearing potential and not using a reliable form of contraception, or who were pregnant or lactating.	AstraZeneca
Gentile 2000	412 patients randomized but only409 patients included in the efficacy analysis. Secondary causes of hyperlipidemia, type 1 DM, elevated CK, BMI >32 kg/m, uncontrolled HTN, MI, CABG, PTCA or established CAD, sensitivity to statins, or taking drugs with the potential for interaction with statins.	MURST funded 60% of study. Otherwise not reported.
Hunninghake 1998	344 patients randomized, efficacy analysis performed on 337 patients. Pregnancy or breast-feeding, secondary hyperlipoproteinemia, uncontrolled endocrine disorders, hepatic or renal impairment, MI, CABG, PTCA, unstable angina 1 month prior to screening, participation in another study, uncontrolled type 2 DM, type 1 DM, taking a drug with the potential for interaction with statins. No numbers provided for exclusion at each step.	Funded by Parke-Davis. One author was employed by Parke-Davis
Illingworth 2001	826 patients randomized. Efficacy analysis performed on 813 patients. Patients receiving immunosuppressants, azole antifungals, or anticoagulants were excluded. No numbers provided for exclusion at each step.	5 of the authors were employed by Merck. Merck employees were thanked for their assistance in preparation of the manuscript.
Insull 2001	Unknown number of patients beginning 8-week dietary phase. 1424 patients randomized and 1378 patients included in efficacy analysis. Pregnant or breastfeeding women, BMI >32, impaired hepatic function, CK elevation, s/p MI, PTCA, CABG, CVA or unstable angina within the last 1 month, secondary hyperlipidemia, significant medical or psychological abnormality, participation in another study, taking a drug with the potential for interaction with statins. No numbers provided for exclusion at each step.	Study supported by Parke-Davis.
Jacotot 1995	134 randomized. Analysis included both on treatment and intention to treat population. Severe forms of hypercholesterolemia and those with impaired renal function were excluded. No details provided on numbers and reasons for excluding patients.	Sandoz funded and participated in trial.
Jones 1998	534 randomized, efficacy analysis performed on 522 patients. Secondary hyperlipidemia, type 1 or uncontrolled type 2 DM, hepatic or renal impairment, uncontrolled HTN, BMI >32 kg/m, MI, CABG, PTCA unstable angina within 3 months of study, hypersensitivity to statins, taking a drug with the potential for interaction with statins. No numbers provided for exclusion at each step.	Funded by Parke-Davis. Parke-Davis employees did participate in some portion of the study.

Evidence Table 4. External Validity of Included Trials

Study Year	Control Group Standard of Care	Length of followup/withdrawals
Fonseca 2005	Yes	12 weeks. 46 (8.2%) rosuva and 27 atorva (4.8%) patients withdrew. 4.8% of rosuva vs 1.8% of atorva patients withdrew due to AEs.
Gentile 2000	Yes	6-week dietary run-in phase 412 randomized, but 409 included in efficacy analysis.
Hunninghake 1998	Yes	Optional 8-week dietary phase, 4-week dietary run-in phase 344 randomized, but 337 included in efficacy analysis.
Illingworth 2001	Yes	4-week dietary run-in. 826 patients randomized, 813 analyzed at 36 weeks.
Insull 2001	Yes	8 weeks dietary run-in. 1424 patients randomized but only 1378 were included in the efficacy analysis at 6 weeks.
Jacotot 1995	Yes	134 randomized. 16 weeks. 11 patients withdrew during trial
Jones 1998	Yes	6-week dietary run-in phase 534 randomized, but 522 included in efficacy analysis.

Evidence Table 4. External Validity of Included Trials

Study Year	Similarity of Population to Disease Population	Number recruited
Jukema 2005	Men and women aged 40 to 80 years with established cardiovascular disease, fasting HDL-c <40 mg/dL at visit 1 and baseline, and triglycerides <=400 mg/dL at visit 1.	Not reported
Marz 1999	Men and women 35-75 years with CHD and elevated LDL-c	Not reported
Nash 1996	Men and women controlled on lovastatin 20 mg qd.	Not reported
Ose 1995	Men and women 70 years or less with hypercholesterolemia	Not reported

Evidence Table 4. External Validity of Included Trials

Study Year	Exclusion Criteria	Funding Source
Jukema 2005	Use of lipid-lowering drugs (including nicotinic acid), dietary supplements or food additives after enrollment, history of hypersensitivity to statins; pregnancy, lactations or childbearing potential without reliable contraceptive use; active arterial disease (unstable angina, MI, TIA, CVA, CABG or angioplasty) within 2 months of entry into the dietary lead-in phase; likely requirement for therapeutic coronary artery intrvention within 6 months of randomizaton; uncontrolled hypertension; glycated hemoglobin >8% at enrollment, history of malignancy; uncontrolled hypothyroidism; homozygous familial hypercholesterolemia or type III hyperlipoproteinemia; history of alcohol and/or drug abuse; active liver disease; serum creatinine >180 µmol/L at enrollment; unexplained creatine kinase >3 times ULN at enrollment; received an investigational drug within 4 weeks before enrollment; serious or unstable medical or psychological conditions that could, in the opinion of the investigator, compromise the subject's safety or successful participation in the trial.	AstraZeneca
Marz 1999	4,097 patients were screened. After the 6 week diet phase, 2,856 patients met the inclusion criteria. Pregnant or breastfeeding women, uncontrolled hypothyroidism, hypertension, DM, or other endocrine disorder, impaired hepatic or renal function, BMI>32, s/p MI, PTCA, CABG, CVA within the last 3 months, moderate to severe CHF, severe hyperlipidemia or hypertriglyceridemia, secondary hyperlipidemia, more than 14 alcoholic drinks per week, taking a drug with the potential for interaction with statins. Other drugs that were not allowed included NSAIDs and digitalis. No numbers provided for exclusion	Study sponsored by Parke-Davis and Pfizer. Employees of these companies were thanked for their continuous scientific support and provision of logistics.
Nash 1996	363 patients screened, 137 patients randomized. (Were large numbers of patients not randomized because their LDL-c upon washout was <160 mg/dl?) Homozygous familial hypercholesterolemia, MI, unstable angina, major surgery or PTCA 6 months prior to study, secondary causes of hyperlipidemia (alcoholism, DM, thyroid disease), pregnant or lactating women and those women who were unwilling to use alternate forms of birth control other than the pill.	Study funded by Sandoz Pharmaceuticals
Ose 1995	432 patients randomized. Analysis for LDL-c reduction did not include 17 patients due to missing or inappropriately done labs. Older than 70, secondary hypercholesterolemia, unstable angina, MI or CABG within 2 months, trigs >350 mg/dl, women not using birth control, history of substance abuse, hepatic or renal impairment, baseline elevations in CK, uncontrolled DM.	Funded by Merck

Evidence Table 4. External Validity of Included Trials

Study Year	Control Group Standard of Care	Length of followup/withdrawals
Jukema 2005	Yes	18 weeks. 8 (3.5%) rosuva and 10 (4.3%) atorva patients withdrew. Number of withdrawals due to AEs not reported, but states the number was low.
Marz 1999	Yes	14 weeks. Withdrawal from study was detailed (e.g. AE or other) and was 9% in both groups.
Nash 1996	Yes	6-week dietary/placebo washout period, 137 patients randomized and completed the study. 8 week study.
Ose 1995	Yes	432 patients randomized and followed for 6 weeks.

Evidence Table 4. External Validity of Included Trials

Study Year	Similarity of Population to Disease Population	Number recruited
Paragh 2004	49 men and women with Frederickson IIa and Ibis hyperlipoproteinaemia with serum trig <4.5 mmol/L and LDL-c >4.1mmol/L	Not reported/49 entered study
Recto 2000	Men or women 21-70 years with an LDL >130 mg/dl	Not reported
Saklamaz 2005	Men and women (mean age 51.7+9.1 years) with type IIa and IIb hyperlipidemia.	Not reported
Schaefer 2003	Patients with a serum LDL-c of>130 mg/dL while off lipid-lowering medication for >=6 weeks (including anion exchange resins, statins, fibric acid derivatives, fish oil, or niacin-containing products) and with evidence of established CHD (coronary artery bypass grafting, angioplasty, documented myocardial infarction, significant coronary artery stenosis as assessed by angiography of >50%, or significantly decreased cardiac perfusion based on cardiac imaging, with and without exercise.	NR/ 99 patients randomized + 97 controls without CHD (196 people total enrolled)
Schulte 1996	Men and women 26-74 years with LDL-c>185 mg/dl and trigs <300 mg/dl.	Not reported

Evidence Table 4. External Validity of Included Trials

Study Year	Exclusion Criteria	Funding Source
Paragh 2004	Patients with diabetes mellitus, previous myocardial infarction, coronary heart disease, liver disease, renal dysfunction (serum creatinine >130 micromol/L) alcoholism, smoking habit, drug addiction, pregnancy, lactation, malignant disease, or had previously received lipid reducing therapy.	Funded by grants from ETT and OTKA Hungary
Recto 2000		Study financially supported by Merck. Simva and placebo were supplied by Merck.
Saklamaz 2005	Patients with endocrine, liver, hepatic, hyyroid, and renal disorders, BMI of less than 30, and alcohol abuse.	Not reported
Schaefer 2003	Evidence of renal impairment, hyperthyroidism, or liver disfunction based on clinical chemistry testing, or had previous adverse reactions to statins.	Funded by investigator-initiated research contracts from Parke-Davis/Pfizer and Otsuka America Pharmaceuticals.
Schulte 1996	120 patients randomized, unclear number completing study. Active liver or gallbladder disease, elevated aminotransferases or other severe disabling disease, women with childbearing potential, drug or alcohol abuse problems, musculoskeletal diseases, or taking drugs with the potential for interaction with statins. No details provided on numbers and reasons for excluding patients.	Funded by Astra

Evidence Table 4. External Validity of Included Trials

Study Year	Control Group Standard of Care	Length of followup/withdrawals
Paragh 2004	Yes	8 months (3 months of treatment, then a 2 month washout period, and then each group was switched over to the corresponding drug for 3 months). No withdrawals were reported, and the study also stated that there were no serious adverse events.
Recto 2000	Yes	6 weeks each treatment. 11 patients withdrew from the study although it was not reported at what time period during the study they withdrew.
Saklamaz 2005	Yes	8 weeks. No withdrawals reported.
Schaefer 2003	Not reported	36 weeks total. Crossover - patients who had received atorv in the first part of the trial were randomized to a different statin, and those who had not been on atorv received in in the second period of testing.
Schulte 1996	Yes	120 patients randomized, unknown completing 10 week study.

Evidence Table 4. External Validity of Included Trials

Study Year	Similarity of Population to Disease Population	Number recruited
Schuster 2004	Patients aged >=18 years with a history of CHD or other established atherosclerotic disease, Type 2 diabetes, or a CHD risk >20% over 10 years, with fasting levels of LDL-c >=115 mg/dL and trigs <400 mg/dL; LDL-c measurements had to be within 15% of each other during the lead-in period.	NR/6508 patients entered dietary phase/3140 randomized
Schwartz 2004	Patients aged >=18 years with type 2 diabetes mellitus or documented atherosclerosis (ie, a history of peripheral vascular disease, coronary artery disease, or cerebrovascular disease). LDL-c levels were >=160 and <250 mg/dL; and trig levels were <= 400 mg/dL.	NR/1233 enrolled in dietary phase/ 383 were randomized.
Stalenhoef 2005	Men and women >=18 years with the metabolic syndrome, defined by presence of at least 3 of the following: abdominal obesity, TG >=150 mg/dL, HDL-c <40mg/dL for men and <50mg/dL for women, blood pressure >=130/85 or receiving antihypertensive treatment, and fasting blood glucose >=110 mg/dL. Also required to have LDL-c >=130 mg/dL and additional multiple risk factors conferring a 10-year CHD risk score of >10%. Patients with diabetes excluded.	1338 screened/ 401 randomized

Evidence Table 4. External Validity of Included Trials

Study Year	Exclusion Criteria	Funding Source
Schuster 2004	Pregnant and lactating women, women not using reliable contraception, patients with a history of homozygous familial hypercholesterolemia or known type III hyperlipoproteinemia, with active arterial disease (eg, unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, or coronary revascularization procedure within 2 months of screening), uncontrolled hypertension, active liver disease or hepatic dysfunction (hepatic transaminases or bilirubin levels >=1.5 times upper limit of normal [ULN]), unexplained serum creatine kinase elevation >3 times ULN, and serum creatinine >220 micromol/L.	Funded by Astra Zeneca, UK. Three authors are employed directly by AstraZeneca, UK.
Schwartz 2004	Pregnant women, patients currently taking concomitant drugs known to affect the lipid profile or to present a potential safety concern, a history of active arterial disease (eg, unstable angina, myocardial infarction, transient ischemic attack, or cerebrovascular accident) or coronary revascularization procedure within 3 months of trial entry, heterozygous or homozygous familial hypercholesterolemia, uncontrolled hypertension, uncontrolled hyperthyroidism, history of malignancy, active liver disease or disfunction indicated by AST or ALT of >= 1.5 times the upper limit of normal (ULN), serum creatine kinase >3 times ULN, serum creatinine >2.5mg/dL, or uncontrolled diabetes (fasting serum glucose >9.99 mmol/L or hemoglobin A1c>9% recorded during the lead-in period).	Supported by AstraZeneca, Delaware. 4 of 7 authors are Astra Zeneca employees.
Stalenhoef 2005	Diabetes; use of lippid-lowering agents within the past 6 months, TG >=500 mg/dL, LDL-c >=250 mg/dL, documented history of CHD or other atherosclerotic disease, history of serious or hypersensitivity reactions to other statins; uncontrolled hypothyroidism; uncontrolled hypertension; acute liver disease or hepatic dysfunction; unexplained serum creatine kinase >3 x ULN; use of prohibited concomitant medications.	

Evidence Table 4. External Validity of Included Trials

Study Year	Control Group Standard of Care	Length of followup/withdrawals
Schuster 2004	Not reported	16 weeks. Groups were split at 8 weeks into groups that either stayed on the original drug or went onto a low dose of rosuv.
Schwartz 2004	Not reported	24 weeks. Doses were up-titrated at 12 and 18 weeks if LDL-c remained >50mg/dL.
Stalenhoef 2005	Yes	

Evidence Table 4. External Validity of Included Trials

Study Year	Similarity of Population to Disease Population	Number recruited
Strandberg 2004	911 men and women >=18 years at high risk for CHD and with primary hypercholesterolemia. Included patients on a starting dose of a lipid-lowering therapy (ie, atorva 10 mg/d, fluva 20 mg/d, prava 20 mg/d, or simva 20 mg/d) who had not yet reached the 1998 JTF goal for LDL-c. Additional inclusion criteria: risk for CHD >20%/10 years in asymptomatic individuals with type 2 diabetes or a history of CHD or other established atherosclerotic disease; or an LDL-c level >135 mg/dL in statin-naive patients or >120 mg/dL in patients using a starting dose of another lipid-lowering drug.	Number recruited not reported; 1024 patients randomized to treatment; 911 patients were in the ITT analysis.
Van Dam 2000	Men or women 18-80 years currently treated with simvastatin 20 or 40 mg qd and LDL-c levels of > 100 mg/dl.	Not reported
Wolffenbuttel 1998	Men and women 18-70 years with an LDL-c between 160 and 240 mg/dl.	Not reported

Evidence Table 4. External Validity of Included Trials

Study Year	Exclusion Criteria	Funding Source
Strandberg 2004	A history of serious adverse events or hypersensitivity to an hMG-CoA reductase inhibitor other than the study drugs; active hepatic disease; homozygous or heterozygous familial hypercholesterolemia (FH); unstable angina; elevated serum creatinine concentration (>220 micromol/L [2.5 mg/dL]) or treatment with a disallowed drug, such as those with known interactions with statins (ie, cyclosporine).	Supported by grants from AstraZeneca Pharmaceuticals, UK.
Van Dam 2000	Pregnant or breastfeeding women, BMI >32, impaired hepatic function, CK elevation, more than 4 alcoholic drinks per day, s/p MI, PTCA, CABG, CVA within the last 3 months, secondary hyperlipidemia, taking a drug with the potential for interaction with statins. No numbers provided for exclusion.	Study financially supported by Parke-Davis and Pfizer.
Wolffenbuttel 1998	78 patients randomized and included in the intention to treat analysis. Untreated HTN, BMI >30 kg/m, DM or other metabolic or endocrine disease, renal or hepatic impairment. No numbers provided for exclusion at each step.	Funded by Parke-Davis. One author was employed by Parke-Davis

Evidence Table 4. External Validity of Included Trials

Study Year	Control Group Standard of Care	Length of followup/withdrawals
Strandberg 2004	Yes	12 week treatment (n=911, ITT) with an optional 36 week follow-up period for select patients from each group (n=387)
Van Dam 2000	Yes	8 weeks. 14% of the randomized patients were not available for follow up. No reasons were given.
Wolffenbuttel 1998	Yes	4-week dietary and placebo run-in. 78 patients were randomized, 78 were analyzed after both treatments

Evidence Table 4. External Validity of Included Trials

Study Year	Similarity of Population to Disease Population	Number recruited
Wolffenbuttel 2005	Men and women with type 2 diabetes who had received treatment for diabetes for at least 3 months, older than 18 years, with fasting LDL-c concentrations of 130 mg/dL in statin-naïve patients or >115 to <=194 in patients who had been taking a statin within the previous 4 weeks. Normal to moderately elevated trig levels, and in acceptable metabolic control.	Not reported

Evidence Table 4. External Validity of Included Trials

Study Year	Exclusion Criteria	Funding Source
Wolffenbuttel 2005	Patients not eligible when they used lipid-lowering drugs after visit 1, or had a history of serious or hypersensitivity reactions to statins; active cardiovascular disease (uncontrolled hypertension >200/>95 mmHg), heart failure NYHA class IV, recent unstable angina, MI, transient ischemic attack, cerebrovascular accident, coronary artery bypass surgery or angioplasty within the previous 2 months, or likely to undergo coronary artery intervention within 6 months after randomization; women who were pregnant or lactating or those not using an effective form of birth control; metabolic abnormalities, such as kidney insufficiency, uncontrolled hypothyroidism, homozygous familial hypercholesterolemia, or familial dysbetalipoproteinemia, active liver disease or liver enzyme [alanine aminotransferase (ALT), aspartate transaminase (AST)] elevations >1.5 ULN and unexplained CK elevations >3 ULN.	AstraZeneca

Evidence Table 4. External Validity of Included Trials

Study Year	Control Group Standard of Care	Length of followup/withdrawals
Wolffenbuttel 2005	Yes	24 weeks. Overall withdrawals not reported. 7% of rosuva and 8% of atorva patients withdrew due to AES.

Evidence Table 4. External Validity of Included Trials

Study Year	Similarity of Population to Disease Population	Number recruited
	Other studies	
4S 1994	Men and women ages 35-70 years with elevated cholesterol and a history of angina pectoris or an acute MI	An unreported number of patients were invited for a brief overview of the study.
A to Z de Lemos 2004	4497 men and women ages 21-80 with either non-ST-elevation acute coronary syndrome or ST elevation MI with a total cholesterol level of 250 mg or lower.	Not reported, 4497 randomized
AFCAPS/ TexCAPS 1998	Healthy men 45-73 years of age and postmenopausal women 55-73 years with average cholesterol levels and no history of a MI.	780,000 patients estimated to be eligible based upon age.
ALLHAT-LLT	Age ≥55 with stage 1 or 2 hypertension and ≥1 CHD risk factor; for those with no known CHD: LDL-C 120-189 mg/dL; for those with known CHD: LDL-C 100-129 mg/dL; triglyceride lower than 350 mg/dL.	10,355

Evidence Table 4. External Validity of Included Trials

Study Year	Exclusion Criteria	Funding Source
	Otl	
4S 1994	7,027 patients were recruited during the 8 week dietary phase of the study. 4,444 patients were enrolled if they were compliant and met the lipid entry criteria. No additional details provided on numbers and reasons for excluding patients.	A member of the project steering committee worked closely with the study monitors at Merck Research Labs in Scandinavia. Merck also provided support with a research grant.
A to Z de Lemos 2004	Receiving statin therapy at the time of randomization, if coronary bypass graft surgery was planned, or if percutaneous coronary intervention was planned within the first 2 weeks after enrollment.	Funded by Merck
AFCAPS/ TexCAPS 1998	102,800 attended screening, 6,605 patients were randomized. No additional details provided on numbers and reasons for excluding patients.	Three of the primary authors are employees of Merck and Co. Two other authors are consultants, speakers and/or funded researchers of Merck and Co. Supported by a research grant from Merck and Co. Spectrum Pharmaceuticals assisted in conducting the trial and Merck and Co helped design the trial and manage the data.
ALLHAT-LLT	Open-label lipid-lowering arm of larger trial in USA. Excluded for current lipid-lowering therapy, large doses of niacin, probucol use, known intolerance or contraindications to statins, significant liver or kidney disease, or known secondary cause of hyperlipidemia. Enrollment discouraged for those whose personal physician already recommended cholesterol-lowering medications.	National Heart, Lung, and Blood Institute; Pfizer; AstraZeneca; Bristol-Myers Squibb

Evidence Table 4. External Validity of Included Trials

Study Year	Control Group Standard of Care	Length of followup/withdrawals
	Otl	
4S 1994	In 1994, there was no evidence to support that lowering LDL-c with a statin lowered the risk of CHD. Yes, although this issue was discussed at length.	5.4 years: 13% of placebo recipients vs. 10% of simvastatin recipients discontinued their medication at the end of the follow up period. Withdrawals prior to trial end were not provided.
A to Z de Lemos 2004	Yes	Up to 24 months. Treatment was discontinued prematurely in 34% of simvastatin only group and 32% of those in placebo first group. Median followup period was 721 days; 22 patients in each treatment group were lost to followup.
AFCAPS/ TexCAPS 1998	yes-primary prevention	5.2 years: 29% of lovastatin recipients withdrew vs. 37% of placebo recipients by the end of the trial. Patients in the placebo group were more likely to be withdrawn as a result of developing CHD or starting lipid-lowering therapy. The discontinuation rates were similar for other reasons in both groups.
ALLHAT-LLT	Yes	4.8 years (mean)

Evidence Table 4. External Validity of Included Trials

Study Year	Similarity of Population to Disease Population	Number recruited
Arntz et al 2000 L-CAD	Inpatients with acute MI or unstable angina	870 screened/735 eligible/135 enrolled
ASCOT	Men and women aged 40-79, no history of CHD, untreated hypertension, total cholesterol concentration <6.5 mmol/L (253 mg/dL), or treated hypertension with systolic blood pressure >140 mm Hg, diastolic blood pressure > 90 mm Hg, plus ≥3 CV risk factors	10.305
Cannon et al 2004 PROVE-IT	Inpatients with acute MI or unstable angina	# screened, eligible not reported, 4162 enrolled
CARDS Colhoun 2004	2838 men and women with no history of cardiovascular disease, LDL of 4.14 or lower, fasting triglyceride of 6.78 or less, and at least one of the following: retinopathy, albuminuria, current smoking, or hypertension.	4053 screened, 2841 randomized.

Evidence Table 4. External Validity of Included Trials

Study Year	Exclusion Criteria	Funding Source
Arntz et al 2000 L-CAD	> age 75, diabetes, postcoronary artery bypass graft, known malignant disease, serious kidney or liver dysfunction, or women of child-bearing age not using a reliable form of contraception.	Supported in part by a grant from Bristol-Myers Squibb.
ASCOT	Lipid-lowering arm of larger trial in UK, Ireland and Scandinavia. Excluded for previous MI, currently treated angina, CV event within 3 months, triglycerides >4.5 mmol/L, heart failure, uncontrolled arrhythmias or any clinically important hematological or biochemical abnormality on routine screening.	Pfizer, New York, NY, USA; Servier Research Group; Leo Laboratories
Cannon et al 2004 PROVE-IT	Coexisting condition that shortened expected survival to less than 2 years, were receiving therapy with any statin at a dose of 80 mg per day at the time of their index event or lipid lowering therapy with fibric acid derivatives or niacin that could not be discontinued before randomization, had received drugs that are strong inhibitors of cytochrome P-450 3A4 whithink the month before randomization or were likely to require such treatment during the study period, had undergone PTCA with the previous 6 months (other than for the qualifying event) or CABG surgery within the previous 2 months or were scheduled to undergo bypass surgery in response to the index event, had factors that might prolong the QT interval, had obstructive hepatobiliary disease or other serious hepatic disease, unexplained elevation in creatinine kinase level that was more than 3 times the ULN and that was not related to MI, or a creatinine level of more than 2.0 mg per deciliter.	Supported by Bristol-Myers Squibb and Sankyo
CARDS Colhoun 2004	Past history of myocardial infarction, angina, coronary vascular surgery, cerebrovascular accident, or severe peripheral vascular disease (defined as warranting surgery).	Partly funded by Pfizer

Evidence Table 4. External Validity of Included Trials

Study Year	Control Group Standard of Care	Length of followup/withdrawals
Arntz et al 2000 L-CAD	Yes	
ASCOT	Yes	3.3 years (median)
Cannon et al 2004 PROVE-IT		
CARDS Colhoun 2004	Yes	Median duration of followup 3.9 years. 1421 atorvastatin, 1398 placebo completed followup for morbidity.

Evidence Table 4. External Validity of Included Trials

Study Year	Similarity of Population to Disease Population	Number recruited
CARE 1996	Men and postmenopausal women 21-75 years of age with average cholesterol levels and a history of an acute MI 3-20 months prior to randomization	An unreported number of patients were invited to participate.
Den Hartog (Pilot Study)	Inpatients with acute MI or unstable angina	# screened, eligible not reported, 100 enrolled, 99 randomized.
Holdaas	Men and women aged 30-75 who received renal or renal/pancreas transplants ≥ 6 months prior, with stable graft function. All using cyclosporine. Total cholesterol 4-9 mmol/L (154-347 mg/dl).	2102
HPS	Men and women, aged 40-80 with elevated total cholesterol (≥135 mg/dl) and substantial 5-year risk of death due to history of coronary disease, occlusive disease of noncoronary arteries, diabetes mellitus, or treated hypertension.	20,536

Evidence Table 4. External Validity of Included Trials

Study Year	Exclusion Criteria	Funding Source
CARE 1996	4,159 patients were enrolled and randomized into the study. No additional details provided on numbers and reasons for excluding patients.	Bristol-Myers Squibb provides study medication, monitors case report forms and supporting documentation to meet regulatory requirements for clinical trials but remains blinded to treatment assignment. They have no access to the data on lipid changes or end points. Bristol-Myers Squibb provided a research grant.
Den Hartog (Pilot Study)	History of hypersensitivity to statins or formulation components, severe heart failure or cardiomyopathy, significant liver disease, significant gastrointestinal disease or abdominal surgery that might adversely influence drug absorption, substance or alcohol abuse, history or present use of any other lipid-lowering or investigational agent, uncontrolled diabetes, thyroid disease, severe renal impairment, dysproteinemia, and primary muscle disease.	Not reported
Holdaas	Patients (number screened NR) in northern Europe, UK and Canada. Excluded for recent MI, or MI > 6 months prior if total cholesterol not within 4-7 mmol/L; already taking statins; familial hypercholesterolemia, acute rejection episodes in previous 3 months, or predicted life expectancy $\leq$ 1 year.	Novartis Pharma AG
HPS	63,603 attended screening in UK, 32,145 started run-in. Ineligible were those already indicated by personal physician for statin therapy, those with chronic liver disease, evidence of abnormal liver, severe renal disease or impaired renal function, inflammatory muscle disease, evidence of muscle problems; concurrent treatment with cyclosporine, fibrates, high-dose niacin; child-bearing potential; severe heart failure; any life-threatening condition other than vascular disease or diabetes, and conditions that might limit long-term compliance. Four-week placebo run-in to measure compliance for long-term study.	UK Medical Research Council; British Heart Foundation; Merck & Co; Roche

Evidence Table 4. External Validity of Included Trials

Study Year	Control Group Standard of Care	Length of followup/withdrawals
CARE 1996	Yes-patients with normal total cholesterol levels.	5 years: 6% of those taking pravastatin discontinued their study medication vs. 14% of those taking placebo. 8% of placebo vs. 2% of pravastatin began taking open-label lipid lowering medication.
Den Hartog (Pilot Study)	Yes	
Holdaas	Yes	5.1 years (mean)
HPS	Yes	5 years (mean)

Evidence Table 4. External Validity of Included Trials

Study Year	Similarity of Population to Disease Population	Number recruited
IDEAL Pederson et al 2005	Men and women aged 80 years or younger with a history of a definite MI and who qualified for statin therapy according to national guidelines.	9689 screened, 8888 randomized
Liem et al 2002 FLORIDA	Inpatients with acute MI or unstable angina	# screened, eligible not reported/ 540 enrolled
LIPID 1998	Men and women ages 31-75 years with a broad range of cholesterol levels and a history of an acute MI or admission for unstable angina in the prior 3 months to 3 years.	An unreported number of patients were invited to participate.
LIPS	Men and women aged 18-80, with successful revascularization; total cholesterol 3.5-7.0 mmol/L (135-270 mg/dl), triglycerides <400 mg/dl before index procedure.	1677
PACT Thompson 2004	3408 men and women age 18 to 85 within 24 hours of onset of acute MI or unstable angina.	Not reported, 3408 randomized

Evidence Table 4. External Validity of Included Trials

Study Year	Exclusion Criteria	Funding Source
IDEAL Pederson et al 2005	Any known contraindications to statin therapy, previous intolerance to statins in low or high doses, liver enzyme levels more than 2 times the ULN, pregnancy or breastfeeding, nephrotic syndrome, uncontrolled diabetes mellitus, uncontrolled hypothyroidism, plasma trig >600 mg/dL, congestive heart failure, hemodynamically important valvular heart disease, GI conditions affecting absorption of drugs, treatment with other drugs that seriously affect the pharmacokinetics of statins, and treatment with other lipid-lowering drugs.	Pfizer
Liem et al 2002 FLORIDA	< age 18, use of lipid-lowering agents within the previous 3 months, high triglyceride level, known familial dyslipidemia, severe renal failure, known hepatic disease, signs and symptoms of severe failure (NYHA Class IV), a scheduled PTCA or CABG, and comedication that influences the sT-segment (digoxin, quinidine or tricyclic antidepressants).	Study financed by an unrestricted grant from AstraZeneca.
LIPID 1998	11,106 patients were recruited and registered. Of those, 9,014 patients were randomized. 2,092 (18%) patients were not randomized (1,333 (12%) were ineligible and 759 (6.8%) did not choose to continue with study.	Bristol-Myers Squibb provided study medication but was not involved with the study design, management of the study or analyzing the data.
LIPS	Patients (number screened NR) from seven countries in Europe, plus UK, Canada, and Brazil. Excluded for sustained systolic blood pressure >180 mm Hg and diastolic blood pressure >100 mm Hg despite therapy; LVEF <30%; history of previous revascularization, severe valvular disease, idiopathic cardiomyopathy or congenital heart disease, severe renal dysfunction, obesity, or malignant or other disease with life expectancy <4 years.	Novartis Pharma AG
PACT Thompson 2004	Taking statin therapy before their event, participation in any other clinical trial or the taking of an investigational drug within the previous 30 days, planned coronary revascularization or cardiac transplantation, severe renal or hepatic disease or other severe disease, drug- or alcohol-related problems, gastrointestinal disease or a history of gastrointestinal surgery that might affect drug absorption, and known hypersensitivity or previous serious adverse reactions to statin therapy. Women of childbearing potential also excluded.	Supported by Bristol-Myers Squibb

Evidence Table 4. External Validity of Included Trials

Study Year	Control Group Standard of Care	Length of followup/withdrawals
IDEAL Pederson et al 2005	Yes (usual-dose simvastatin)	4.8 years (median)
Liem et al 2002 FLORIDA	Yes	
LIPID 1998	Yes-providers were instructed to continue with usual care of the patient including open-label lipid lowering medication if indicated.	6.1 years: 19% of pravastatin recipients and 24% of placebo recipients discontinued their study medication. The majority of placebo recipients discontinued their treatment assignments to begin therapy with open-label lipid lowering medication.
LIPS	Yes	3.9 years (median)
PACT Thompson 2004	Yes	30 days; 85 patients (2%) lost to followup

Evidence Table 4. External Validity of Included Trials

Study Year	Similarity of Population to Disease Population	Number recruited
PREVEND IT Asselbergs 2004	864 residents of one city in the Netherlands, ages 28-75 with persistent microalbuminuria, blood pressure <160/100 mm Hg, and no use of antihypertensive medication, and a total cholesterol level <309 mg/dL, or <193 mg/dL in case of previous myocardial infarction, and no use of lipid-lowering medication.	40,856 screened, 864 randomized
PROSPER	Men and women aged 70-82 with pre-existing vascular disease or raised risk due to smoking, hypertension or diabetes.; cholesterol 155-350 mg/dl (4-9 mmol/L), triglycerides <530 mmol/L and good cognitive function	5804
Schwartz et al 2001 MIRACL	Inpatients with acute MI or unstable angina	# screened, eligible not reported/ 3086 enrolled
Stone et al 2005	Men and women age <85 years, with fasting total cholesterol 180-250 mg/dL, and objective evidence of coronary disease.	597 screened, 300 randomized

Evidence Table 4. External Validity of Included Trials

Study Year	Exclusion Criteria	Funding Source
PREVEND IT Asselbergs 2004	Creatinine clearance <60% of the normal age-adjusted value and use of ACE inhibitors or angiotensin II receptor antagonists.	Dutch Kidney Foundation, Netherlands Heart Foundation, and Bristol-Myers Squibb
PROSPER	Patients (number screened NR) from Scotland, Ireland, and the Netherlands. Excluded for CV event ≤6 months, any overnight surgery, poor cognitive function, NYHA class III or IV, history of malignancy within 5 years significant arrhythmia, implanted pacemaker, organ transplant recipient, current lipid-lowering treatment or cyclosporin use, current alcohol or drug abuse, any medical condition or travel that prevents optimal participation; abnormal lab findings, including for hemoglobin, thyroid stimulating hormone, glucose, platelet count, white blood cell count, serum creatinine, aminos.	Bristol-Myers Squibb, USA
Schwartz et al 2001 MIRACL	Total cholesterol level at screening >270 mg/dL, if coronary revascularization was planned or anticipated at the time of screening, evidence of Q-wave acute MI within the preceding 3 months; CABG within preceding 3 months, PTCA within preceding 6 months, left bundle-branch block or paced ventricular rhythm, severe heart failure (NYHA class IIIb or IV), concurrent treatment with other lipid-regulating agents (except niacin 500 mg/day), vitamin E (except at doses 400 IU/day or less), or drugs associated with rhabdomyolysis in combination with statins, severe anemia, renal failure requiring dialysis, hepatic dysfunction (alanine aminotransferase greater than 2 times ULN), insulin-dependent diabetes, pregnancy or lactation.	Supported by a grant from Pfizer Inc. Pfizer provided the atorvastatin and matching placebo used.
Stone et al 2005	An acute coronary syndrome within 1 month of study entry, coronary revascularization procedure within 6 months of study entry, congestive heart failure greater than NYHA class III, significant valvular heart disease, cigarette smoking withn 2 months of study entry, and a resting 12-lead ECG that was not interpretable to detect the presence of ischemia.	NIH and Pfizer

Evidence Table 4. External Validity of Included Trials

Study Year	Control Group Standard of Care	Length of followup/withdrawals
PREVEND IT Asselbergs 2004	Yes	4 years.
PROSPER	Yes	3.2 years (mean)
Schwartz et al 2001 MIRACL	Yes	
Stone et al 2005	Yes (low-dose lovastatin if needed)	1 year

Evidence Table 4. External Validity of Included Trials

Study Year	Similarity of Population to Disease Population	Number recruited
Wanner et al 2005	Men and women ages 18-80 years with type 2 diabetes and receiving maintenance hemodialysis.	1522 entered run-in, 1255 randomized
WOSCOPS 1995	Men, 45-64 years of age with high cholesterol and no history of MI.	160,000 men

Evidence Table 4. External Validity of Included Trials

Study Year	Exclusion Criteria	Funding Source
Wanner et al 2005	LDL-c <80 mg/dL or more than 190 mg/dL, trig >1000 mg/dL; liver-function values more than 3 X ULN or equal to those in patients with symptomatic hepatobiliary cholestatic disease; hematopoietic disease or systemic disease unrelated to end-stage renal disease; vascular intervention, congestive heart failure, or MI within the 3 months preceding the period of enrollment; unsuccessful kidney transplantation; and hypertension resistant to therapy.	Pfizer
WOSCOPS 1995	160,000 recruited, 81,161 men attended first visit, 20,914 attended the second visit, 13,654 attended the third visit, 6,595 patients were randomized. No additional details provided on numbers and reasons for excluding patients.	Role unknown. Supported by a research grant from Bristol-Myers Squibb.

Evidence Table 4. External Validity of Included Trials

Study Year	Control Group Standard of Care	Length of followup/withdrawals
Wanner et al 2005	Yes	4 years (median)
WOSCOPS 1995	yes-primary prevention	4.9 years: placebo vs prava recipient % withdrawals - cumulative withdrawal rates At 1 year: 14.9 vs 15.5%; year 2: 19.1 vs 19.4%; year 3: 22.5 vs 22.7%; year 4: 25.2 vs 24.7~~%,~~ year 5: 30.8 vs 29.6%.

Evidence Table 5. Atherosclerotic progression trials

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction from baseline	Primary Endpoint
Herd et al. 1997 Lipoprotein and Coronary Atherosclerosis Study (LCAS)	Randomized, double-blind, placebo-controlled, not intent to treat analysis	429 men or women 35-75 years with ≥1 coronary atherosclerotic lesion causing 30-75% diameter stenosis	Fluvastatin 20 mg bid or placebo bid. Cholestyramine up to 12 g/day was given to those with LDL-c≥160 mg/dl after dietary phase.	2.5 years	146.2 ± 20.1 mg/dl (3.78 mmol/L)	22.5% (fluvastatin alone)	Within patient per-lesion change in MLD of qualifying lesion as assessed by coronary angiography.
Furberg et al. 1994 Asymptomatic Carotid Artery Progression Study (ACAPS)	Randomized, double-blind, placebo-controlled, intent to treat analysis	919 men or women 40-79 years with early carotid atherosclerosis and elevated LDL-c	Lovastatin 20 mg qpm or placebo qpm. Lovastatin was titrated to 40 mg qd if LDL-c >90-100 mg/dl. Warfarin 1 mg qd or placebo qd.	3 years (last 300 randomized only received 33 months of follow up	156.6 mg/dl (4 mmol/L)	28%	Progression of a summary measure via B-mode ultrasonography: the mean of the maximum IMT measurements from the 12 walls, near and far, of the common carotid, the bifurcation, and the internal carotid arteries bilaterally measured by B-mode ultrasonography.
Waters et al. 1994 The Canadian Coronary Atherosclerosis Intervention Trial (CCAIT)	Randomized, double-blind, placebo-controlled, not intent to treat analysis	331 men or women up to 70 years at higher risk for CHD events with diffuse CHD and TC 220-300 mg/dl.	Lovastatin 20 mg qpm or placebo qpm. Lovastatin was titrated to 40 and then 40 mg bid if LDL-c >130 mg/dl.	2 years	173 mg/dl (4.5 mmol/L)	29%	Comparison between groups for coronary change score (per-patient mean of the MLD for all lesions measured as determined by coronary angiography

BID=twice a day, CHD=coronary heart disease, IMT=intimal-medial thickness, MLD=minimum lumen diameter, MI=myocardial infarction, qpm=every evening

Evidence Table 5. Atherosclerotic progression trials

Author Year Study Name	Primary Endpoint Results (clinical health outcome only)	Clinical Outcomes Measured	Clinical Outcome Results	Comments/Conclusions
Herd et al. 1997 Lipoprotein and Coronary Atherosclerosis Study (LCAS)	N/A	Any cardiac, cerebrovascular, peripheral vascular, and fatal events. Also time to first CABG, PTCA, MI, hospitalization for USA or all-cause mortality	Any cardiac morbid or fatal event occurred in 12.7% of fluvastatin vs. 18.9% placebo. Time to these events showed a trend towards benefit with fluvastatin. Need for revascularization was reduced with fluvastatin 8.9% vs. 13.4% with placebo. No statistical significance provided.	LCAS was not designed with sufficient power to detect differences in clinical events. However, there was a trend observed in favor of fluvastatin. In this study, there were 909 patients screened, but only 429 randomized. The major reasons were for lipid ineligibility and lack of cooperation. There were some minor difference in baseline characteristics between groups. Fair-poor in quality to determine differences in clinical events.
Furberg et al. 1994 Asymptomatic Carotid Artery Progression Study (ACAPS)	N/A	One of the secondary endpoints in the trial was to determine the treatment effects on major atherosclerotic events.	5 (all nonfatal MI) major cardiovascular events occurred in the lovastatin vs. 14 in the lovastatin-placebo groups (4-CHD deaths, 5-strokes, 5-nonfatal MI). p=0.04, ARR=2 events/100 persons, NNT=5. Overall mortality: One death in lovastatin vs. 8 deaths in lovastatin-placebo groups p=0.02, ARR 1.5 events/100 persons, NNT=65. All 6 cardiovascular deaths occurred in lovastatin-placebo groups.	The secondary objective of major atherosclerotic events was significantly reduced in the lovastatin vs. the lovastatin-placebo groups in patients with early carotid atherosclerosis. Fair-good in quality to determinine differences in clinical events.
Waters et al. 1994 The Canadian Coronary Atherosclerosis Intervention Trial (CCAIT)	N/A	Cardiac and noncardiac events, mortality and revascularization were reported in the safety analyis.	Patients had one or more events: lovastatin 14 patients (2 deaths from cardiac causes, 5 MI, 8 USA), placebo 18 patients (1 death from cardiac causes, 6 MI, 13 USA) (NS)	CCAIT was not designed with sufficient power to detect differences in clinical events. However, there was a trend in favor of lovastatin. Mean lovastatin dose=36 mg/d and 69% met NCEP goal). Fair-poor in quality to assess differences in clinical events.

BID=twice a day, CHD=coronary heart disease, IMT=intimal-medial thickness, MLD=minimum lumen diameter, MI=myocardial infarction, qpm=every evening

Evidence Table 5. Atherosclerotic progression trials

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction from baseline	Primary Endpoint
Blankenhorn et al. 1993 The Monitored Atherosclerosis Regression Study (MARS)	Randomized, double-blind placebo-controlled, not intent to treat analysis	270 men or women younger than 70 years and CHD in 2 coronary segments 50% or >	Lovastatin 80 mg qpm or placebo qpm.	2.2 years	151 mg/dl (3.91 mmol/L)	38%	Per-patient change in percent diameter stenosis between groups as determined by quantitative coronary angiography.
Jukema et al. 1995 The Regression Growth Evaluation Statin Study (REGRESS)	Randomized, double-blind, placebo-controlled, not intent to treat analysis	885 men with clinical evidence of CHD and TC 155-310mg/dl (4-8 mmol/L)	Pravastatin 40 mg qpm or placebo qpm.	2 years	166 mg/dl (4.3 mmol/L)	29%	Change in average mean segment diameter per patient and change in average minimun obstruction diameter per patient determined by coronary arteriography.
Pitt et al. 1995 Pravastatin Limitation of Atherosclerosis in Coronary Arteries (PLAC- I)	Randomized, double-blind, placebo-controlled, not intent to treat analysis	408 men or women with CHD as evidenced by 1 or > stenosis ≥50% or recent MI or PTCA and LDL-c ≥130 mg/dl	Pravastatin 40 mg qpm or placebo qpm.	3 years	164 mg/dl (4.24 mmol/L)	28%	Change in average MLD and change in percent diameter stenosis as determined by coronary arteriography.

BID=twice a day, CHD=coronary heart disease, IMT=intimal-medial thickness, MLD=minimum lumen diameter, MI=myocardial infarction, qpm=every evening

Evidence Table 5. Atherosclerotic progression trials

Author Year Study Name	Primary Endpoint Results (clinical health outcome only)	Clinical Outcomes Measured	Clinical Outcome Results	Comments/Conclusions
Blankenhorn et al. 1993 The Monitored Atherosclerosis Regression Study (MARS)	N/A	Cardiac and noncardiac events, mortality and coronary revacularization were reported in the safety analysis.	22 lovastatin vs. 31 placebo recipients had one or more of the following: MI, PTCA, CABG, CHD death or hospitalization for USA. (NS) Also no difference in overall death.	MARS was not designed with sufficient power to detect differences in clinical events. However there was a trend in favor of lovastatin. Fair-poor in quality to assess differences in clinical events.
Jukema et al. 1995 The Regression Growth Evaluation Statin Study (REGRESS)	N/A	Prespecified clinical events: Fatal and nonfatal MI, CHD death, nonscheduled PTCA or CABG, Stroke or TIA, and all-cause death.	After 2 years of treatment, 89% of pravastatin vs. 81% of placebo recipients were free from clinical events (p=0.002). Although nonsignificant, there were 12 nonfatal MI in the placebo vs. 7 in the pravastatin groups (ARR 1.2/100 persons, NNT=83). Unscheduled PTCA were reduced significantly in the pravastatin vs. placebo groupg (p=0.004, RRR=57%, ARR 5.8/100 persons, NNT=17).	REGRESS prespecified analysis of clinical events. The only signficant difference in individual events was the reduced need for unscheduled PTCA in the pravastatin vs. placebo groups. This signficant reduction accounted for the overall reduction in new clinical events in the pravastatin group. Difficult to tell if intent to treat population was included in overall clinical event analysis. Fair in quality to assess differences in clinical events.
Pitt et al. 1995 Pravastatin Limitation of Atherosclerosis in Coronary Arteries (PLAC- I)	N/A	Prespecified clinical events: Fatal and nonfatal MI, nonfatal infarction or CHD death, nonfatal infarction or death from any cause and total clinic events (nonfatal MI, nonfatal completed stroke, death PTCA and CABG).	There were 17 MI in placebo vs. 8 in pravastatin ($P \leq 0.05$, RRR=60%, ARR=4.5/100 persons, NNT=22). Although not statistically significant, there were 37 PTCA in placebo vs. 25 in pravastatin. A total of 81 events occurred in placebo vs. 55 in pravastatin (NS).	PLAC-1 prespecified analysis of clinical events. The only significant difference in individual events was a reduction in the rate of MI in the pravastatin vs. placebo groups. All randomized patients were included in the clinical event analysis. Fair in quality to assess differences in clinical events, although a relatively small study population.

BID=twice a day, CHD=coronary heart disease, IMT=intimal-medial thickness, MLD=minimum lumen diameter, MI=myocardial infarction, qpm=every evening

Evidence Table 5. Atherosclerotic progression trials

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction from baseline	Primary Endpoint
Crouse et al. 1995 Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II)	Randomized, double-blind, placebo-controlled, not intent to treat analysis	Men and women with CHD as evidenced by ≥ stenosis of 1 or > coronary artery or history of MI with elevated LDL-c.	Pravastatin 20 mg qpm or placebo qpm. If LDL-c was not <110 mg/dl pravastatin was increased to 40 mg qpm.	3 years	167.5 mg/dl (4.33 mmol/L)	28%	Change in the mean of the maximal IMT measurement across time determined by B-mode ultrasonography.
Salonen et al. 1995 Kuopio Atherosclerosis Prevention Study (KAPS)	Randomized, double-blind, placebo-controlled, not intent to treat analysis	Men 44-65 years with LDL-c≥4 mmol/L (155 mg/dl). Only 10% had history of MI (Primary prevention study)	Pravastatin 40 mg qpm or placebo qpm.	3 years	185 mg/dl (4.8 mmol/L)	27.40%	Rate of carotid atherosclerotic progression measured as the linear slope over annual ultrasound examinations in the average of maximum carotid IMT of the far wall of up to 4 arterial segments.
Sato et al. 2001	Randomized, unblinded, intent to treat analysis for clinical events	329 men and women <70 years with CHD documented by coronary angiography with normal cholesterol.	Pravastatin 10 mg qpm.	2 years	200 mg/dl (TC) (5.2 mmol/L). LDL-c not provided	8.5% (TC)	Mean segment diameter and minimum obstruction diameter were used to evaluate progression as assessed by coronary angiography.

BID=twice a day, CHD=coronary heart disease, IMT=intimal-medial thickness, MLD=minimum lumen diameter, MI=myocardial infarction, qpm=every evening

Evidence Table 5. Atherosclerotic progression trials

Author Year Study Name	Primary Endpoint Results (clinical health outcome only)	Clinical Outcomes Measured	Clinical Outcome Results	Comments/Conclusions
Crouse et al. 1995 Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II)	N/A	Prespecified clinical events: Fatal coronary events or nonfatal MI, all-cause mortality, all deaths plus nonfatal MI.	For the combined endpoint of nonfatal MI and any death, there was a significant reduction in the pravastatin vs. placebo group (5 vs. 13, respectively). P=0.04,RRR=61%, ARR=1/100 persons, NNT=10	PLAC-II prespecified analysis of clinical events. The only significant difference was in the combined endpoint of nonfatal MI plus any deaths. Not much detail provided in clinical event section, for observation of other clinical events that were not signficantly reduced with pravastatin. Fair-poor in quality to assess difference in clinical events. Small sample size.
Salonen et al. 1995 Kuopio Atherosclerosis Prevention Study (KAPS)	N/A	Clinical events were reported spontaneously.	The number of cardiovascular events reported during the trial were not statistically significantly different between groups. However, there was a trend to less clinical cardiovascular events in the pravastatin group, primarily MI.	KAPS was not designed to sufficiently determine differences in clinical cardiac events between groups. However, there was a trend in favor of pravastatin. Fair-poor in quality to determine differences in clinical events between groups.
Sato et al. 2001	N/A	Prespecified clinical events: Fatal and nonfatal MI, CHD death, nonscheduled PTCA or CABG, Stroke or TIA, and all-cause death. (using criteria defined by REGRESS)	The incidence of clinical events was lower in the pravastatin groups vs. placebo but this difference was not significant. All-cause mortality was significantly reduced in the pravastatin vs. placebo groups (p=0.043)	Prespecified clinical events. There was a trend to a reduction in clinical cardiac events in the pravastatin vs. placebo groups, however the difference was not significant. There was a significant reduction in overall mortality with pravastatin vs. placebo. Fair in quality to assess difference in clinical events. Small sample size.

BID=twice a day, CHD=coronary heart disease, IMT=intimal-medial thickness, MLD=minimum lumen diameter, MI=myocardial infarction, qpm=every evening

Evidence Table 5. Atherosclerotic progression trials

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction from baseline	Primary Endpoint
Simoons 1994 Multicentre Anti-Atheroma Study	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	404 men and women 30-67 years with 2 or > coronary artery segments occluded and hyper-cholesterolemia	Simvastatin 20 mg qpm or placebo qpm.	4 years	169 mg/dl (4.38 mmol/L)	31%	Per-patient average of mean lumen diameters of all coronary segments(diffuse atherosclerosis) and the per-patient average of MLD of all segments that were atheromatous at baseline, follow up or both (focal atherosclerosis) as assessed by coronary angiography.
Bestehorn et al. 1997 Multicenter Coronary Intervention Study (CIS)	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	254 men 30-55 years with at least 3 coronary segments with a lumen diameter of ≥20% and TC of 207-350 mg/dl.	Simvastatin 20 mg qpm or placebo qpm. Simvastatin was increased to 40 mg qpm if LDL-c>90 mg/dl	2.3 years	164.5 mg/dl (4.25 mmol/L)	35%	Global change score and the per-patient mean change in MLD as assessed by coronary angiography.
Teo et al. 2000 The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT)	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	460 men and women 21 year or >, atherosclerosis in 3 or > coronary segments, TC 160-240 mg/dl	Simvastatin 10 mg qpm or placebo qpm and enalapril 2.5 mg bid or placebo (2X2). Simvastatin could be titrated to 40 mg qpm.	47.8 months	130 mg/dl (3.36 mmol/L)	30.50%	Changes in absolute mean segment lumen diameter, absolute minimum segment lumen diameter, and maximum percent lumen diameter stenosis.

BID=twice a day, CHD=coronary heart disease, IMT=intimal-medial thickness, MLD=minimum lumen diameter, MI=myocardial infarction, qpm=every evening

Evidence Table 5. Atherosclerotic progression trials

Author Year Study Name	Primary Endpoint Results (clinical health outcome only)	Clinical Outcomes Measured	Clinical Outcome Results	Comments/Conclusions
MAAS Investigators 1994 Multicentre Anti-Atheroma Study	N/A	Clinical events were reported spontaneously.	After 4 years, there was no difference in clinical events between groups. There were a greater number of MI in the simvastatin vs placebo groups. There were more revascularizations in the placebo vs. simvastatin groups. Neither of these were statistically different. Overall, there were 40 cardiac events in the simvastatin vs. 51 in the placebo groups (NS).	There were no stastical differences in clinical events in the simvastain vs. placebo groups. Fair to poor in quality to assess differences in clinical event due to duration of trial, however was a relatively small sample size.
Bestehorn et al. 1997 Multicenter Coronary Intervention Study (CIS)	N/A	Clinical events were reported spontaneously.	There were no significant differences in clinical events with simvastatin vs. placebo. Overall, there were 15 events in the simvastatin and 19 in the placebo groups.	There were no stastical differences in clinical events in the simvastain vs. placebo groups. Fair to poor in quality to assess differences in clinical event due to duration of trial, however was a relatively small sample size.
Teo et al. 2000 The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT)	N/A	Prespecified clinical events: death, MI, stroke, hospitalization for angina, revascularization and cancer.	The only signficant difference in clinical events between simvastatin and placebo was a reduction in the number of revascularizations (6 vs. 12%, p=0.020and angioplasties (3 vs. 9% p=0.02).	There was a significant reduction in revascularization, specifically angioplasty in the simvastatin vs. placebo. No differences were noted in any other clinical events. Fair in quality to assess diffferences in clinical events since clinical events were prespecified.

BID=twice a day, CHD=coronary heart disease, IMT=intimal-medial thickness, MLD=minimum lumen diameter, MI=myocardial infarction, qpm=every evening

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction	Primary Endpoint
Serruys PW. et al. 1999 Fluvastatin Angiographic Restenosis Trial (FLARE)	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	1054 men or women with symptomatic or ischaemia producing coronary lesions amenable to angioplasty and an LDL-c <230 mg/dl (6 mmol/L)	Fluvastatin 40 mg bid or placebo bid	40 weeks	153 mg/dl (3.96 mmol/L)	33%	Angiographic restenosis as assessed by quantitative coronary angiography as the loss of MLD during followup.
Weintraub WS. et al. 1994 The Lovastatin Restenosis Trial	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	404 men or women in whom angioplasty of a native vessel with a stenosis of 50-99% was successful.	Lovastatin 40 mg bid or placebo bid.	6 months	130 mg/dl (3.4 mmol/L)	42%	Extent of restenosis of the index lesion as assessed by angiography.

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Primary Endpoint Results (provided only if it is a clinical health outcome)	Other Clinical Outcomes Measured	Other Clinical Outcome Results	Comments/Conclusions
Serruys PW. et al. 1999 Fluvastatin Angiographic Restenosis Trial (FLARE)	N/A	*Prespecified clinical endpoints:* Death, MI, CABG or re-intervention	Major cardiac events occurred in 92 fluvastatin vs. 99 placebo recipients (p=0.74). When death and MI were combined, there was a significant reduction in the fluvastatin vs. placebo groups (p=0.03 ARR=2.5/100 persons NNT=39)	Although not sufficiently powered to determine differences in clinical events, the combined endpoint of death/MI was significantly reduced in the fluvastatin vs. placebo groups s/p successful balloon angioplasty. The composite of major clinical events which included death/MI/CABG/re-intervention was not different between groups (p=0.74). Fair-poor in quality for assessment of differences in clinical events between groups (relatively short follow up period, insufficiently powered).
Weintraub WS. et al. 1994 The Lovastatin Restenosis Trial	N/A	Clinical events were spontaneously reported.	There were no differences in the rate of death, stroke, CABG, re-intervention (angioplasty) between groups. There was a trend towards more MI in the lovastatin vs. placebo groups (p=0.058)	There was no difference in the rate of restenosis between groups. There was also no difference in the rate of major clinical cardiac events in the lovastatin vs. placebo groups. There was a trend towards more MI in the lovastatin vs. placebo groups. Fair-poor in quality for assessment of differences in clinical events between groups (relatively short followup period, small sample size).

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction	Primary Endpoint
The Post Coronary Artery Bypass Graft Trial 1997 Post Coronary Artery Bypass Graft Trial (PCABG)	Randomized, intent to treat analysis for clinical events	1351 men or women 21-74 years with history of CABG 1-11 years prior and a baseline LDL-c of 130-175 mg/dl and at least 1 patent graft as seen on angiography	Aggressive LDL-c lowering with lovastatin 40 mg qpm titrated to 80 mg qpm (goal LDL-c < 85) or moderate LDL-c lowering with lovastatin 2.5 mg qpm titrated to 5 mg qpm (goal LDL-c <140 mg/dl). Warfarin 1 mg qd or placebo qd (titrated to 4 mg qd or INR of 2 or >) (2X2 design)	4.3 years	154 mg/dl (4 mmol/L)	37-40% yearly in the aggressive group. 13-15% yearly in the moderate group	Mean percentage per patient of grafts with a decrease of 0.6 mm or > in lumen diameter of initially patent grafts as assessed by angiography
Kleeman A. et al. 1999 The Cholesterol Lowering Atherosclerosis Trial (CLAPT)	Randomized, unblinded treatment, blinded angiographic endpoint, intent to treat for clinical events.	226 men 18-70 years scheduled for PTCA with a second vessel stenosis of >20% and LDL-c >135 mg/dl	Lovastatin 20 mg qpm or usual care. Lovastatin was titrated up to 80 mg qpm for LDL-c >120 mg/dl	2 years	181 mg/dl (4.7 mmol/L)	29%	Angiographic progression and restenosis. Change in mean segment diameter (diffuse coronary atherosclerosis) of nondilated and dilated segments and MLD (focal coronary atherosclerosis) of dilated lesions at 2 years as assessed by angiography

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Primary Endpoint Results (provided only if it is a clinical health outcome)	Other Clinical Outcomes Measured	Other Clinical Outcome Results	Comments/Conclusions
The Post Coronary Artery Bypass Graft Trial 1997 Post Coronary Artery Bypass Graft Trial (PCABG)	N/A	*Prespecified clinical endpoints as a composite and individually:* Death from cardiovascular or unknown causes, nonfatal MI, stroke, CABG or PTCA	There were no differences in the composite or individual clinical outcomes between treatments. There was a 29% reduction of revascularization in the aggressive lovastatin group vs. the moderate lovastatin group but did not reach statistical significance criteria in this study (p=0.03)	There was a significant difference in the rate of atherosclerotic progression favoring aggressive LDL-c lowering with lovastatin. There were no differences in composite or individual clinical outcomes between groups. There was a trend toward the aggressive lovastatin group in reducing revascularization. Fair in quality to assess differences in degree of LDL-c lowering and its effect on clinical outcomes, although no difference was noted.
Kleeman A. et al. 1999 The Cholesterol Lowering Atherosclerosis Trial (CLAPT)	N/A	*Pre-specified or defined clinical events:* MI, re-PTCA, PTCA of another lesion, or death	There were 62 serious clinical events in lovastatin vs. 75 in usual care (NS). The only significant difference was a reduction in the 2nd or 3rd re-PTCA favoring lovastatin (p=0.02)	There were no differences in the rate of clinical events in the lovastatin vs. placebo groups with the exception of 2nd or 3rd re-PTCA (p=0.02). Fair in quality to assess differences in clinical events between groups. (small sample size, unblinded)

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction	Primary Endpoint
Bertrand ME. et al. 1997 Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty (PREDICT)	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	695 men or women 25-75 years and TC 200-310 mg/dl who had undergone successful PTCA	Pravastatin 40 mg qpm or placebo qpm	6 months	155 mg/dl (4 mmol/L)	23%	Minimum lumen diameter as assessed by coronary angiography
Flaker GC. et al. 1999 Subgroup of CARE	Randomized, double-blind, placebo-controlled, intent to treat analysis. (Subgroup analysis of revascularized patients in CARE)	2245 men or women with history of MI and <240 mg/dl and revascularization	Pravastatin 40 mg qpm or placebo qpm	5 years	138.4 mg/dl (3.6 mmol/L)	28%	Reduction in clinical cardiovascular events (CHD death or nonfatal MI, fatal and nonfatal MI, revascularizations and stroke)

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Primary Endpoint Results (provided only if it is a clinical health outcome)	Other Clinical Outcomes Measured	Other Clinical Outcome Results	Comments/Conclusions
Bertrand ME. et al. 1997 Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty (PREDICT)	N/A	Secondary endpoints: restenosis rate and clinical events (death, MI, target vessel revascularization)	There were no differences in clinical restenosis or events between groups (80 events in placebo vs. 74 events in pravastatin)	There were no differences in the rate of clinical events or clinical restenosis in the pravastatin (74 events) vs. placebo (80 events) groups (death, MI, CABG, re-PTCA of target lesion). Fair in quality to assess differences in clinical events between groups (Relatively short follow up period)
Flaker GC. et al. 1999 Subgroup of CARE	Pravastatin reduced the incidence of CHD death or nonfatal MI (RRR=36%, 95% CI 17-51%, p<0.001), fatal or nonfatal MI (RRR=39%, 95% CI 16-55%, p<0.002), and stroke (RRR=39%, 95% CI 3-62, p=0.037). There was a trend towards benefit with pravastatin in reducing repeat revascularization (RRR=18%, 95% CI 1-33%, p=0.068)	Subgroup analysis of CARE of revascularized patients.	See primary endpoint results.	Pravastatin significantly reduced clinical events (CHD death, nonfatal MI and stroke) in previously revascularized patients. There was a trend to reduced revascularizations in the pravastatin vs. placebo groups. Good in quality to assess differences in clinical events between groups.

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction	Primary Endpoint
Pitt B. et al. 1999 The Atorvastatin vs. Revascularization Treatment (AVERT)*	Randomized, unblinded, intent to treat analysis for clinical events	341 men or women 18-80 years with 50% stenosis of 1 or > coronary arteries and an LDL-c ≥115 mg/dl	Atorvastatin 80 mg qpm or PTCA	18 months	Approximately 140-148 mg/dl (3.6-3.8 mmol/L)	46% (22% of all patients were on lipid-lowering drugs prior to randomization with no washout)	Reduction in ischemic events: death from cardiac causes, resuscitation after cardiac arrest, nonfatal MI, CVA, CABG, PTCA, or hospitalization for angina.
Marz W. et al. 1999 The Target Tangible Trial (TT)*	Randomized, unblinded, intent to treat analysis for clinical events	2856 men or women 35-70 years with CHD and an LDL-c ≥130 mg/dl	Atorvastatin 10 to 40 mg qpm or simvastatin 10-40 mg qpm	14 weeks	188 mg/dl (4.9 mmol/L	Atorvastatin 10 mg=37.6% vs simvastatin 10 mg=31.9%	Safety (adverse events and laboratory events) and efficacy (LDL-c reduction)
Pravastatin Multinational Study Group 1993*	Randomized, double-blind, placebo-controlled, intent to treat analysis for clinical events	1062 men or women 20-69 years with 2 or > risk factors and a TC of 200-300 mg/dl (5.2-7.8 mmol/L)	Pravastatin 20 mg qpm or placebo. After 13 weeks, pravastatin could be doubled to 40 mg qpm	26 weeks	181 mg/dl (4.69 mmol/L)	26.01%	Change in serum lipids (TC, LDL-c, HDL-c, triglycerides)

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Primary Endpoint Results (provided only if it is a clinical health outcome)	Other Clinical Outcomes Measured	Other Clinical Outcome Results	Comments/Conclusions
Pitt B. et al. 1999 The Atorvastatin vs. Revascularization Treatment (AVERT)*	22 (13%) of the atorvastatin vs. 37 (21%) of the angioplasty group experienced ischemic events (p=0.048) NS as adjusted for interim analysis. Events making up the majority of the trend in favor of atorvastatin: CABG and hospitalization for angina	Time to first ischemic event	Time to first ischemic event was longer in the atorvastatin vs. angioplasty group (p=0.03 95% CI 5-67 RRR=36%)	Unequal baseline characteristics between groups (sex, antiplatelets/anticoagulants, and location of target lesion). Approximately 70% of patients in the angioplasty group received a statin. Mean LDL-c 119 mg/dl in angioplasty group vs. 77 mg/dl in atorvastatin group. There was a trend in reduction in clinical events with atorvastatin vs. angioplasty, however CABG and hospitalization for angina accounted primarily for this difference. Angioplasty was the main variable in this study. Poor in quality for assessment of differences in clinical events between groups.
Marz W. et al. 1999 The Target Tangible Trial (TT)*	Serious adverse events were not different between groups. Serious cardiovascular adverse events occurred in 19 atorvastatin vs. 21 simvastatin patients (p<0.05 if 1-sided test applied).	N/A	N/A	Serious cardiovascular adverse events were significantly higher in the simvastatin vs. atorvastatin group, p<0.05 if the 1-sided test is used.
Pravastatin Multinational Study Group 1993*	N/A	Reported clinical events as part of safety analysis, although cardiovascular events were predefined as fatal or requiring prolonged hospitalization.	Significantly more serious cardiovascular events were reported in the placebo (13) vs. pravastatin (1) groups (p<0.001 ARR 2.2/100 persons NNT=44)	There was a significant reduction in serious cardiovascular events in the pravastatin vs. placebo groups. Fair in quality to assess differences in clinical events between groups (relatively short follow up period).

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Study Characteristics	Patient Characteristics	Intervention	Study Duration (mean)	Mean Baseline LDL-c	Percent LDL-c Reduction	Primary Endpoint
Serruys PW. et al. 2002 Lescol Intervention Prevention Study (LIPS)	Randomized, double-blind, intention-to-treat analysis for all randomized	1677 Men or women 18-80 years status post successful percutaneous coronary intervention (PCI) and TC between 135 and 270 mg/dl (calculated 3.5-7.0 mmol/L).	Fluvastatin 40 mg bid or placebo bid	3.9 years	131 mg/dl (3.4 mmol/L)	27% (median)	Survival time free of major coronary events (any death, nonfatal MI, repeat revascularization). Divergence seen at 1.5 years.

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty

Evidence Table 6. Post-revascularization and miscellaneous trials

Author Year Study Name	Primary Endpoint Results (provided only if it is a clinical health outcome)	Other Clinical Outcomes Measured	Other Clinical Outcome Results	Comments/Conclusions
Serruys PW. et al. 2002 Lescol Intervention Prevention Study (LIPS)	Time to major coronary events was 1558 days in the fluvastatin vs. 1227 days in the placebo group (p=0.01). 181 (21.4%) of fluvastatin vs. 222 (26.7%) of placebo recipients (p=0.01, 95% CI 0.64-0.95, ARR 5.2/100 persons, NNT=19)	Major coronary events excluding repeat revascularizations occurring within the first 6 months	Rate of major coronary events (excluding repeat revascularizations) diverged at 6 months and showed an extended event-free survival time in the fluvastatin vs. placebo groups (p<0.001, 95% CI 0.54-0.84)	Time to major coronary events was significantly prolonged in the fluvastatin vs. placebo group. Adverse effects were not statistically different between groups. Fair-good in quality for assessment of differences in clinical events between groups (Number of diabetics was not equal between groups).

*Studies included in the miscellaneous category. CABG=coronary artery bypass graft; CVA=cerebrovascular accident; MI=myocardial infarction; MLD=minimal lumen diameter; PTCA=percutaneous transluminal coronary angioplasty