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Month/Year of Review: March 2012
PDL Class: Statins & combos

Date of Last Review: February 2010
Source Document: HRC Report

Current Preferred Agents:
Atorvastatin (Lipitor®)
Simvastatin
Lovastatin
Pravastatin

Current Non-Preferred Agents:
Fluvasatin, Fluvastin XL
Rosuvastatin (Crestor®)
Lovastatin (Altoprev® ER)
Pitavastatin (Livalo®)
Niacin/Lovastatin (Advicor®)
Ezetimibe/Simvastatin (Vytorin®)

Previous Conclusions (February 2010):[1]

Adults

- Evidence supports the ability of atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin to improve coronary heart disease clinical outcomes.
- Atorvastatin, pravastatin and simvastatin have been shown to reduce strokes.
- While these drugs improve clinical outcomes the absolute risk reduction is small.
- Fair to good strength evidence demonstrates that when statins are provided in doses that are approximately equipotent, a similar percent reduction in low-density lipoprotein cholesterol can be achieved, along with comparable increases in high-density lipoprotein cholesterol.
- In adult patients with no known coronary heart disease there were still no head to head trials of statins or fixed dose combination products containing a statin (and another lipid lowering drug) for health outcomes.
- There are no clinical outcome studies for fixed dose combination products containing a statin and another lipid lowering agent.
- No evidence supports differences between Statins in adverse effects in sub-populations by race and ethnicity, age, gender or comorbidity.
- Niacin containing fixed dose combination products have a higher rate of discontinuation due to flushing.
- Studies in patients with diabetes did not have higher rates of adverse events.
- Potential for interactions with CYP 3A4 inhibitors (atorvastatin, lovastatin, and simvastatin).
- Potential for interaction with CYP 2C9 inhibitors (fluvastatin).
- Statin-fibrate combination increases risk of musculoskeletal-related adverse events compared with monotherapy.

Children

- Trials of statins (simvastatin, atorvastatin, lovastatin, pravastatin, and rosuvastatin) have been conducted primarily in children with familial hypercholesterolemia and other familial dyslipidemias in trials of less than one year duration.
- The comparison of the fixed dose combination product ezetimibe/simvastatin vs. simvastatin demonstrated a 54% reduction in low-density lipoprotein for the combination vs. 38% for simvastatin alone.
- Studies of statins in children have not been conducted with long enough follow-up to assess for outcomes related to cardiovascular mortality and morbidity.
- No trials have evaluated statins in children with diabetes or obesity.
- There is insufficient data to determine rates of adverse events or harms in children.

Reason for Review:

Since the last OR review in 2010 pitavastatin (Livalo®) was FDA approved to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol. Also,new safety alerts including new restrictions, contraindications and dose limitations for simvastatin were released by the FDA to reduce the risk of muscle injury. This update will examine the place in therapy for pitavastatin, and identify any other new relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines for consideration.

Issues:

- Is there any new comparative evidence showing a significant difference between statins in their ability to reduce the risk of nonfatal myocardial infarcation, coronary heart disease, mortality, stroke, or hospitalization?
- Is there any reliable data that pitavastatin is safer or more effective than other lipid-lowering agents?
- Is there any differences in effectiveness or harms in subpopulations between pitavastatin and other currently available statins?

Conclusions:

Reductions in cardiovascular and cerebrovascular risk are not unique to any specific statin and have been demonstrated with many of the available medications. Decreases in the risk for acute coronary syndromes, coronary procedures, strokes, and other coronary outcomes have been demonstrated. There is no comparative effectiveness data that the most recent FDA-approved agent, pitavastatin, is more effective or safer than other lipid-lowering agents for managing the risk of cardiovascular events or death in patients with hypercholesterolemia. In June 2011 the FDA issued a safety warning regarding the highest dose of simvastatin. New dosing restrictions warrant further management to avoid muscle injury associated with simvastatin 80mg and associated drug drug interaction and simvastatin 80mg should not be initiated in new patients.

Recommendations:

1. Make pitavastatin a non-preferred statin medication on the PDL due to lack of long term clinical outcomes data and no apparent advantages over currently available statins.
2. Due to the increased risk of muscle damage associated with simvastatin 80mg, recommend implementing a prospective dose limit.

Methods:

A MEDLINE Ovid search was conducted using all statins including: hyperlipidemia, hypercholesterolemia, cardiovascular disease, hydroxyl-3-methyglutaryl coenzyme A (HMG COA) reductase inhibitors, statin, Zocor, Lipitor, Mevacor, Pravachol, Lescol, Livalo, and Crestor. The search was limited to randomized controlled trials and meta-analysis, English language, and to studies conducted in humans from February 2010 to present. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The Food and Drug Administration (FDA) website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Systematic Reviews:

There were several systematic reviews published within this class review period that focused on various sub-populations.[2-4] See Appendix A for details of selected review abstracts.

- In July 2010, the Cochrane Collaboration[2] produced a review of evidence-based literature to assess the effectiveness and safety of statins in children with familial hypercholesterolemia. The search included randomized and controlled clinical trials up to March 11, 2010 for patients up to 18 years of age comparing a statin to a placebo or diet alone. There were 19 potentially eligible studies of which they included eight randomized placebo-controlled trials (897 participants). The authors concluded that statin treatment is an efficient lipid-lowering therapy in children with familial hypercholesterolemia. Statins reduced the mean LDL at all time points and clinical adverse events were similar in both groups. It seems to be safe in the short term but long-term safety is unknown. Children treated with statins should be carefully followed up by their pediatricians. Large long-term randomized controlled comparative trials are needed to establish the long-term safety of statins in children.

- A meta-analysis published in November 2011 by Tonelli M et al.[4] evaluated the efficacy of statins for primary prevention in people at low cardiovascular risk defined as observed an observed 10-year risk of less than 20% for cardiovascular-related death or nonfatal myocardial infarction. The review concluded that Statins were found to be efficacious in preventing death and cardiovascular morbidity in people at low cardiovascular risk based on 29 trials. Reductions in relative risk for all cause mortality were similar to those seen in patients with a history of coronary artery disease and significantly lower among patients receiving a statin than among placebo (pooled

RR 0.90, 95% confidence interval [CI] 0.84-0.97, I^2=2.0%; NNT = 239) Patients in the statin group were also significantly less likely to have a nonfatal myocardial infarcation (RR 0.64, 95% CI 0.49 to 0.84; NNT = 153) and nonfatal stroke (RR 0.81, 95% CI 0.68 to 0.96; NNT = 335). The trials were individually assessed for a risk of bias and were found to exhibit a moderate risk.

New Guidelines:

There were no new guidelines regarding statin use during this class review period. In May 2010, the Canadian Agency for Drugs and Technologies in Health (CADTH) released a guideline review on Statin administration following acute myocardial infarctions based on a limited literature search on key health technology assessments resources.[6] The overall findings include the following:

- High-dose statins, defined as those aimed at reducing LDL level below 70mg/dL, significantly reduce the risk of mortality or major cardiovascular event compared to a standard lipid lowering regimens.
- The five systemic reviews estimated the high-dose statins reduced the risk of mortality by 19-28% over less intensive lipid-lower regimens, with mean follow-up durations of one to two years.
- One systemic review estimated that the survival benefit of intensive statin treatment after an acute coronary episode was seen as early as four months after the event, reaching statistical significance at 12 months.
- One of the systemic reviews defined "intensive statin therapy" as atorvastatin 80mg/day, simvastatin 80mg/day or rosuvastatin 20-40mg/day.
- All identified guidelines recommend the administration of statins following acute coronary episodes (including MI), with most specifying long-term therapy; however, there were differences regarding recommended dosage.
- A New Zealand guideline recommends starting all patients on the equivalent of 20-40mg/day of simvastatin after MI, whereas three others recommended intensive statin therapy defined as equivalent of simvastatin 80mg/day.
- The Scottish Intercollegiate Guideline Network guideline for coronary heart disease recommends a stepwise approach: patients with cardiovascular events should be started on simvastatin 40mg/day, stepping up to atorvastatin 20, 40, and finally 80mg/day if LDL-C level targets were not met. LDL-C treatment targets also varied between guidelines, ranging from less than 70mg/dL to less than 116mg/dL.

New Randomized Controlled Trials (RCT):

The MEDLINE search retrieved 88 full citations. After a review of citations and abstracts, 27 studies were identified for assessment. After review for relevant patient populations, interventions, and outcomes, twelve new randomized control trials (RCT) were identified, excluding the study supporting approval of Livalo® (Appendix B). Eleven of these studies compared the different statins or a statin in combination with ezetimibe (Zetia®) or fenofibrate with various dosing strategies to achieve the treatment goal. None of these studies evaluated comparative effectiveness in long term cardiovascular outcomes.

New FDA Indications:
None identified.

New FDA safety alerts:

Medication	Alert Date	FDA Alert
Simvastatin (Zocor®) Ezetimibe/ Simvastatin (Vytorin®)	06/08/2011	**New restrictions, contraindications and dose limitations to reduce the risk of muscle injury :** **Revised Contraindications:** Posaconazole, gemfibrozil, cyclosporine and Danazol are added as new drugs to be contraindicated with simvastatin. **New restrictions including dose limitations:** • Do not exceed 10mg simvastatin with amiodarone, verapamil and diltiazem. (Note: These drugs are contraindicated with Simcor as Simcor is only available with 20mg and 40mg of simvastatin.) • Do not exceed 20mg simvastatin daily with amlodipine and ranolazine. • Simvastatin 80mg should only be used in patients who have been taking this dose for 12 months or more and have not experienced any muscle toxicity. It should not be prescribed to new patients. • *12/15/2011 update*: Simvastatin dose limitation has been increased from 10mg to 20mg when con-administered with amiodarone.
Ezetimibe/ Simvastatin (Vytorin®)	October 2011	**Warnings and precautions** **Myopathy/Rhabdomyolysis:** Vytorin therapy should be discontinued if marked elevated CPK levels occur or myopathy suspected. **Liver Enzymes:** There have rare post marketing reports of fatal and non-fetal hepatic failure on patients taking statins, including simvastatin. **Adverse Reactions:** **Post-marketing experience:** There have been rare post marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated… **Patient counseling information:** **Liver enzymes:** …All patients treated with Vytorin should be advised to report promptly any symptoms that may indicate liver injury, including… **Patient package insert:** **"What are the possible side effects of Vytorin?"…:** Your doctor should do blood tests to check your liver before you start taking Vytorin and if you have any…

New FDA-approved drugs:
Pitavastatin (Livalo®)

Clinical Findings:
Pitavastatin is the 7th HMG CoA reductase inhibitor approved by the FDA. It has been available in several countries for many years and various previous studies are available describing the use of pitavastatin. However, the studies were mainly done in foreign countries (e.g., Japan, South Korea). Data cannot necessary be extrapolated to U. S population as many sub-populations and different ethnicities can respond differently to HMGs. Studies performed in the Western countries which allowed it to gain FDA approval only evaluated its efficacy based on the intermediate outcome of decreasing serum LDL. In a dose-ranging study[23] (n = 251) pitavastatin 1 mg, 2 mg and 4mg each given once daily in those with primary hyperlipidemia, led to LDL-C reductions of -32%, -36%, and -43%, respectively, at week 12. Comparative data are available with pitavastatin vs. other HMGs. Pitavastatin was compared to other statins in non-inferiority trials and found to be effective in lowering LDL. One pitavastatin vs. atorvastatin (Lipitor®) trial[23] (n = 817) found that at 12 weeks pitavastatin 2 mg QD and atorvastatin 10 mg QD, has similar LDL-C lowering capacity (-38%); pitavastatin 4 mg QD and atorvastatin 20 mg QD were also similar (LDL-C reductions of -45% and -44%, respectively). In another similar trial[20] (n = 843), the LDL-C reductions with pitavastatin 2 mg QD and simvastatin 20 mg QD (Zocor®) were similar (-39% and -35%, respectively); the respective percentages for pitavastatin 4 mg QD and simvastatin 40 mg QD were -44% and -43%. Other trials[21, 22] are available, but none of the pivotal data compared atorvastatin or simvastatin utilized the 80 mg maximum dose.

Clinical Pharmacology[23]: Pitavastatin is a HMG-CoA reductase inhibitor, which is a rate-determining enzyme involved with biosynthesis of cholesterol, in a manner of competition with the substrate so that it inhibits cholesterol synthesis in the liver. As a result, the expression of LDL-receptors followed by the uptake of LDL from blood to liver is accelerated and then the plasma TC decreases. Further, the sustained inhibition of cholesterol synthesis in the liver decreases levels of very low density lipoproteins. It is indicated for patients with primary hyperlipidemia and mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total-C, LDL-C, apo B, TG, and to increase HDL-C.

Drug Safety[23]:

Contraindications: Known hypersensitivity to the components of pitavastatin. Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels. Do not administer pitavastatin to women who are pregnant or may become pregnant. Pitavastatin should not be given to nursing mothers and in those receiving cyclosporine. Pitavastatin is contraindicated in those with active liver disease.

Warnings/Precautions:

Skeletal muscle effects: Pitavastatin should be prescribed with caution in those with predisposing factors for myopathy. Such factors include advanced age (aged > 65 years), renal impairment, and inadequately treated hypothyroidism. The risk of myopathy may be increased with concurrent administration of fibrates or lipid-modifying doses of niacin. Use pitavastatin with caution in patients with impaired renal function, in elderly patients, or when used concomitantly with fibrates or lipid-modifying doses of niacin. Discontinue pitavastatin if markedly elevated creatine kinase (CK) levels occur or myopathy is diagnosed or suspected.

Liver enzyme abnormalities and monitoring: Increases in serum transaminases (asparatate aminotranferase [AST]/serum glutamic-oxaloacetic transaminase, or alanine aminotranferase [ALT]/serum glutamic-pyruvic transaminase) have been reported with HMGs, including pitavastatin. In most instances, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. In placebo-controlled, Phase 2 studies, ALT > 3 times the upper limit of normal was not observed in the placebo, pitavastatin 1 mg or Livalo 2 mg groups. One out of 202 patients (0.5%) given pitavastatin 4 mg had ALT > 3 times the upper limit of normal. Liver enzyme tests should be performed before and 12 weeks after both therapy initiation and dose increases; monitor periodically thereafter (e.g., semiannually).

Geriatrics: Of the 2,800 patients randomized to pitavastatin 1 mg to 4 mg in controlled clinical studies, 1,209 (43%) were aged > 65 years. No significant differences in efficacy or safety were noted between elderly patients and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

Clinical Efficacy:

Relevant Endpoints: LDL- lowering and HDL- raising ability

Reduction in nonfatal myocardial infarcation

Coronary Artery Disease, stroke, and mortality

Withdrawals due to adverse events;

Serious adverse events

Study Endpoints: LDL reduction

Evidence Table

Ref./Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy; Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR / NNH[3]	Quality Rating[4]; Comments
1. Ose L et al[20] MC, prospective, RCT, DB, DD PG	1. Pitavastatin (P) 2mg 2. Pitavastatin (P) 4mg 3. Simvastatin (S) 20mg 4. Simvastatin (S) 40mg	Men and non-pregnant, non-lactating women aged 18-75 years of age with primary hyper-cholesterolemia or combined dyslipidemia	P2: 307 P4: 319 S20: 107 S40: 110	12 weeks	• Endpoint mean % LDL change (SD): P2 : -39 (14.6); S20: -35 (15.5) P4: -44 (14.5); S40: -42.8 (15.8) • Adjusted mean difference (95% CI): P2 vs. S20: 4.1 (0.8-7.3); p = 0.014 (noninferiority) P4 vs. S40: 1.1 (-2.1- 4.3); p=0.509 (noninferiority) • Target attained according NCEP criteria (n %): P2: 215 (70.0); S20: 69 (64.5) CI: -16.0 - 4.9; P = 0.297 (noninferiority) P4: 253 (79.6); S40: 86 (78.2) CI: -10.3 - 7.5; P = 0.762 (noninferiority) • Target attained according to EAS criteria (n %): P2: 183 (59.6); S20: 52 (48.6) CI: -22.0 to -0.1; P = 0.049 (noninferiority) P4: 239 (75.2); S40: 83 (75.5) CI: -9.0 - 9.6; P = 0.950 (noninferiority)	NA	• Any ADEs (n %): P2: 110 (35.4) S20: 36 (33.6) P4: 103 (32.2) S40: 30 (27.3) • Any serious ADEs (n %): P2: 3 (1.0) S20: 2 (1.9) P4: 4 (1.3) S40: 2 (1.8) • Any treatment-related ADEs (n %): P2: 52 (16.7) S20: 15 (14.0) P4: 42 (13.1) S40: 9 (8.2) • DC due to ADEs (n %): P2: 13 (4.2) S20: 3 (2.8) P4: 8 (2.5) S40: 1 (0.9) *CI and p values were not reported.	NA	Fair • The chosen simvastatin doses of 20mg and 40mg were based on assumption they are expected to be equipotent and they are the most commonly prescribed. • Patients with significant CV disease such as MI, CAD or PAD, bypass graft surgery were excluded in the study. • Female is majority gender cross all study groups and concurrent HRT, oral contraceptives are allowed; however if the baseline concurrent medication uses are comparable is unknown. • The study design used 3:1 ratio, made it less powerful to detect ADEs in the simvastatin groups; therefore unable to directly compare ADEs between pitavastatin and simvastatin. • Clinical outcomes such as mortality, CV mortality or CV mordality were not reported.

2.Gumprech J et al[21] RCT, DB, DD PG	1. Pitavastatin (P) 4mg 2. Atorvastatin (A) 20mg 3.Atorvastatin (A) 40mg	18 -75 years with type 2 diabetes with HbA1C ≤ 7.5% on either oral or insulin therapy	Core study: P4: 279 A20: 139 Extension study: P4: 141 A20:64 A40: 7	Core study 12 weeks Extension Study: 44 weeks	• Endpoint mean % LDL change (n, mean ±SD) at week 12: P4: 274, -40.8±19.6 A20: 136, -43.3±16.4 CI: -2.33 (- 6.18 to 1.52) • Endpoint mean % LDL change n, mean ±SD at week 16: P4: 141, -43.0±18.6 A20 or A40: 71, -42.9±20.3 CI: 0.11 (-5.23 to 5.44) • Endpoint mean % LDL change n, mean ±SD (CI) at week 44: P4: 141; -41.0±19.1 A20 or A40: 71, -41.4±21.2 CI: -0.02 (-5.46 to 5.41)	NA	• Any ADEs (n %): P4: 100 (36.4) A20: 54 (39.4) • Any serious ADEs (n %): P4: 4 (1.5) A20: 4 (2.9) • DC due to ADEs (n %): P4: 7 (2.5) A20: 5 (3.6)	NA	Fair • Patients completing the core study could continue on stud drugs if lipid targets not reached by wk8 for further 4 wks (extension study); however it is not statistically powered • The atorvastatin group had a slightly longer mean duration o f dyslipidemia and more pts had a duration of DM at least 5 yrs compared with pitavastatin group. • P value was not reported for endpoint analyses. • Clinical outcomes such as mortality, CV mortality or CV mordality were not reported.
3.Eriksson M[22] RCT, DB, DD PG	1. Pitavastatin (P) 4mg 2. Simvastatin (S) 40mg	18-75 y/o with ≥ of the following CV risk factors: smoking; BP ≥ 140/90 or on BP tx; HDL ≤40mg/dL; family hx of CHD in a male or female 1st degree relative < 55 or <65 respectively; age >45 in men or > 55 in women. An HDL>60 mg/dL was considered to offset 1 risk factor	P4: 233 S40: 119	12 weeks	• Endpoint mean % LDL change n, mean ±SD: P4: 233, -44.0±12.8 S40: 119, -43.8±14.4 CI: 0.31 (-2.47 to 3.09) P = 0.829 (noninferiority) • Selected 2ndary endpoint mean % LDL change n, mean ±SD: HDL-C: P4: 223, 6.8±12.6 S40: 118, 4.5±12.1 CI: -2.30 (-4.91 to 0.30); P: 0.083 TG: P4: 223, -19.8±21.3 S40: 118, -14.8±29.7 CI: 5.23 (0.15 to 10.30) P = 0.044	NA	• Any ADEs (n %): P4: 119 (51.1) S40: 60 (50.4) • Any serious ADEs (n %): P4: 4 (1.7) S40: 5 (4.29) • DC due to ADEs (n %): P4: 9 (3.9) S40: 6 (5.0) • Tx related ADEs (n %): P4: 33 (14.2) S40: 26 (21.8)		Fair • More than 2/3 of the patients in each group fell into moderate NCEP risk category. • There were slightly more pts in simvastatin group on a CCB than pitavastatin • Short term study • Clinical outcomes such as mortality, CV mortality or CV mordality were not reported.

[1]**Study design abbreviations:** DB = double-blind, DD = double dummy, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR =absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

Common Drug-Related Adverse Events and Drug Interactions:[23]

Adverse events**:** The most frequent adverse reactions (rate ≥ 2.0% in at least one marketed dose) were myalgia, back pain, diarrhea, constipation and pain in extremity.

Drug interactions**:** Livalo is metabolized by glucuronidation via liver UGTs with subsequent formation of pitavastatin lactone. There is only minimal metabolism by the cytochrome P450 system (marginally metabolized by CYP2C9 and to a lesser extent by CYP2C8). Pitavastatin is associated with some drug-drug interactions or monitoring recommendations. Coadministration of cyclosporine with pitavastatin is contraindicated. Protease inhibitors, such as lopinavir, ritonavir, rifampin, and erythromycin increase the level of pitavastatin. Concurrent use of fibrates and niacin should be cautiously due to increased risk of skeletal musde effects.

DOSE & AVAILABILITY:

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
1mg	Tablet	Oral	Once daily	CrCl 30-59: start 1mg, max. 2mg/day; CrCl 10-29: not defined.	None.	Not established	None	Pitavastatin can be taken with or without food at any time of the day. Doses greater than 4mg daily were associated with an increased risk of severe myopathy; do not exceed 4mg daily.
2mg	Tablet	Oral	Once daily					
4mg	Tablet	Oral	Once daily					

PHARMACOKINETICS

Parameter	Result
Oral Bioavailability	51% for oral solution. High fat meal (50% fat content) decreases C_{max} by 43%, not AUC.
C_{max}	1 hour
Protein Binding	99%
Elimination	15% in urine and 79% in feces
Half-Life	12 hours
Metabolism	Primarily by glucuron-idation via liver UGTs. Marginally by CYP2C9, and to a lesser extent by CYP2C8

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Appendix A: Abstract of new Systematic Review

1. **Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Strandberg T, Tonstad S, Gylling H. Statins for children with familial hypercholesterolemia. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD006401. DOI: 10.1002/14651858.CD006401.pub2.**

Abstract

Background**:** Familial hypercholesterolemia is one of the most common inherited metabolic diseases; the average worldwide prevalence of heterozygous familial hypercholesterolemia is about 1 in 500. Diagnosis of familial hypercholesterolemia in children is based on two measurements of low-density lipoprotein cholesterol level above 4.0 mmol/L or a DNA-based analysis. Coronary stenosis has been detected in men with familial hypercholesterolemia as young as 17 years old and in women with familial hypercholesterolemia at 25 years of age. Atherosclerosis and its clinical complications occur prematurely, especially in men, thus lifelong hypolipidemic measures, started in childhood, are needed to reduce the risk of cardiovascular diseases. In children with familial hypercholesterolemia, diet has been the main mode of treatment. Anion exchange resins, such as cholestyramine and colestipol, have also been found to be effective but are generally considered unpalatable and therefore poorly tolerated. Since the 1990s statin trials have been carried out among children with familial hypercholesterolemia (aged 7 to 17 years), and statins reduced their serum low-density lipoprotein cholesterol levels by 23% to 40%. The safety of statins among children is not well known even though statins seem to be safe and well-tolerated in adults.

Objectives: To assess the effectiveness and safety of statins in children with familial hypercholesterolemia.

Search methods: Relevant trials were identified from the Group's Inborn Errors and Metabolism Trials Register and Medline. Date of most recent search: 11 March 2010

Selection criteria: Randomized and controlled clinical trials including participants up to 18 years old comparing a statin to placebo or to diet alone.

Data collection and analysis: Two authors independently assessed studies for inclusion and extracted data.

Main results: We found 19 potentially eligible studies of which we included eight randomized placebo-controlled trials (897 participants). Statins reduced the mean low-density lipoprotein cholesterol concentration at all time points. There was no difference between serum aspartate and alanine aminotranferase or creatine kinase concentrations at any time-point. The risks of myopathy and clinical adverse events were also similar in both groups. In one study simvastatin was shown to improve flow-mediated dilation of the brachial artery, and in another study treatment with pravastatin for two years induced a significant regression in carotid intima-media thickness.

Authors' conclusions**:** Statin treatment is an efficient lipid-lowering therapy in children with familial hypercholesterolemia. It seems to be safe in the short term but long-term safety is unknown. Children treated with statins should be carefully followed up by their pediatricians. Large long-term randomized controlled trials are needed to establish the long-term safety of statins in children.

2. Efficacy of statins for primary prevention in people at low cardiovascular risk: a meta-analysis.

Tonelli M, Lloyd A, Clement F, Conly J, Husereau D, Hemmelgarn B, Klarenbach S, McAlister FA, Wiebe N, Manns B; Alberta Kidney Disease Network. CMAJ. 2011 Nov 8;183(16):E1189-202. Epub 2011 Oct 11.

Abstract

Background*:* Statins were initially used to improve cardiovascular outcomes in people with established coronary artery disease, but recently their use has become more common in people at low cardiovascular risk. We did a systematic review of randomized trials to assess the efficacy and harms of statins in these individuals.

Methods: We searched MEDLINE and EMBASE (to Jan. 28, 2011), registries of health technology assessments and clinical trials, and reference lists of relevant reviews. We included trials that randomly assigned participants at low cardiovascular risk to receive a statin versus a placebo or no statin. We defined low risk as an observed 10-year risk of less than 20% for cardiovascular-related death or nonfatal myocardial infarction, but we explored other definitions in sensitivity analyses.

Results: We identified 29 eligible trials involving a total of 80,711 participants. All-cause mortality was significantly lower among patients receiving a statin than among controls (relative risk [RR] 0.90, 95% confidence interval [CI] 0.84-0.97) for trials with a 10-year risk of cardiovascular disease < 20% [primary analysis] and 0.83, 95% CI 0.73-0.94, for trials with 10-year risk < 10% [sensitivity analysis]). Patients in the statin group were also significantly less likely than controls to have nonfatal myocardial infarction (RR 0.64, 95% CI 0.49-0.84) and nonfatal stroke (RR 0.81, 95% CI 0.68-0.96). Neither metaregression nor stratified analyses suggested statistically significant differences in efficacy between high-and low-potency statins, or larger reductions in cholesterol.

Interpretation**:** Statins were found to be efficacious in preventing death and cardiovascular morbidity in people at low cardiovascular risk. Reductions in relative risk were similar to those seen in patients with a history of coronary artery disease.

Appendix B: Abstracts of new randomized controlled trials

1. **Ezetimibe + simvastatin versus doubling the dose of simvastatin in high cardiovascular risk diabetics: a multicenter, randomized trial (the LEAD study). Bardini G, Giorda CB, Pontiroli AE, Le Grazie C, Rotella CM. Cardiovasc Diabetol. 2010 May 21;9:20.**

Abstract

Background: The primary goal of therapy in patients with hypercholesterolemia and coronary heart disease (CHD) is reducing low-density lipoprotein cholesterol (LDL-C). This was a multicenter, randomized, double-blind, double-dummy study in patients with type 2 diabetes mellitus (T2DM).

Methods: Adult patients with T2DM and CHD (N = 93) on a stable dose of simvastatin 20 mg with LDL-C >or= 2.6 mmol/L (100 mg/dL) and <or= 4.1 mmol/L (160 mg/dL) were randomized to ezetimibe 10 mg plus simvastatin 20 mg (EZ + simva 10/20 mg) or simvastatin 40 mg for 6 weeks. Percent change in LDL-C, high-density lipoprotein cholesterol, and triglycerides was assessed.

Results: EZ + simva 10/20 mg produced a significantly greater change from treated baseline compared with simvastatin 40 mg in LDL-C (-32.2% vs -20.8%; $p < 0.01$) and total cholesterol (-20.6% vs -13.2%; $p < 0.01$). A greater proportion of patients achieved LDL-C < 2.6 mmol/L with EZ + simva 10/20 mg than with simvastatin 40 mg, but this was not statistically significant (78.4% vs 60%; odds ratio = 2.81; $p = 0.052$). Changes in high-density lipoprotein cholesterol and triglycerides were similar between treatments. Both treatments were generally well-tolerated.

Conclusions: These results demonstrate that EZ + simva 10/20 mg may provide a superior alternative for LDL-C lowering vs doubling the dose of simvastatin to 40 mg in hyperlipidemic patients with T2DM and CHD. In addition, the combination therapy may provide an alternative treatment for patients who require further LDL-C reduction than they can achieve with simvastatin 20 mg alone.

2. **Ezetimibe added to atorvastatin compared with doubling the atorvastatin dose in patients at high risk for coronary heart disease with diabetes mellitus, metabolic syndrome or neither. Conard S, Bays H, Leiter LA, Bird S, Lin J, Hanson ME, Shah A, Tershakovec AM. Diabetes Obes Metab. 2010 Mar;12(3):210-8.**

Abstract

Aim*:* Type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS) are both associated with increased risk for atherosderotic coronary heart disease (CHD). Thus, it is useful to know the relative efficacy of lipid-altering drugs in these patient populations.

Methods*:* A double-blind, parallel group trial of adult patients with hypercholesterolaemia at high-CHD risk receiving atorvastatin 40 mg/day compared atorvastatin 40 mg plus ezetimibe 10 mg (ezetimibe) vs. doubling atorvastatin to 80 mg. This post hoc analysis reports lipid efficacy results in patients grouped by diagnosis of T2DM, MetS without T2DM or neither. Per cent change from baseline at week 6 was assessed for LDL-C, total cholesterol, HDL-C , non-HDL-C , Apo A-I, Apo B and triglycerides. Safety was monitored through clinical and laboratory adverse events (AEs).

Results: Compared with doubling atorvastatin, atorvastatin plus ezetimibe resulted in greater reductions in LDL-C, triglycerides, Apo B, non-HDL-C, total cholesterol and lipid ratios in the T2DM, MetS and neither groups. Treatment effects were of similar magnitude across patient groups with both treatments, except triglycerides, which were slightly greater in the T2DM and MetS groups vs. neither group. Changes in HDL-C , Apo A-I and high sensitivity C-reactive protein (hs-CRP) were comparable for both treatments in all three groups. Safety and tolerability profiles were generally similar between treatments and across patient groups, as were the incidence of liver and musde AEs.

Conclusions: Compared with doubling atorvastatin to 80 mg, addition of ezetimibe to atorvastatin 40 mg produced greater improvements in multiple lipid parameters in high-CHD risk patients with T2DM, MetS or neither, consistent with the significantly greater changes observed in the full study cohort (dinical trial # NCT00276484).

3. **Achieving cholesterol targets by individualizing starting doses of statin according to baseline low-density lipoprotein cholesterol and coronary artery disease risk category: the CANadians Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (CanACTFAST) study. Ur E, Langer A, Rabkin SW, Calciu CD, Leiter LA; CanACTFAST Study Investigators. Can J Cardiol. 2010 Feb;26(2):**
80-6.

Abstract

Background: Despite an increasing body of evidence on the benefit of lowering elevated levels of low-density lipoprotein cholesterol (LDL-C), there is still considerable concern that patients are not achieving target LDL-C levels.

Objectives: The CANadians Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (CanACTFAST) trial tested whether an algorithm-based statin dosing approach would enable patients to achieve LDL-C and total cholesterol/high-density lipoprotein cholesterol (TC/HDL-C) ratio targets quickly.

Methods: Subjects requiring statin therapy, but with an LDL-C level of 5.7 mmol/L or lower, and triglycerides of 6.8 mmol/L or lower at screening participated in the 12-week study, which had two open-label, six-week phases: a treatment period during which patients received 10 mg, 20 mg, 40 mg or 80 mg of atorvastatin based on an algorithm incorporating baseline LDL-C value and cardiovascular risk; and patients who achieved both LDL-C and TC/HDL-C ratio targets at six weeks continued on the same atorvastatin dose. Patients who did not achieve both targets received dose uptitration using a single-step titration regimen. The primary efficacy outcome was the proportion of patients achieving target LDL-C levels after 12 weeks.

Results: Of 2016 subjects screened at 88 Canadian sites, 1258 were assigned to a study drug (1101 were statin-free and 157 were statin-treated at baseline). The proportion of subjects who achieved LDL-C targets after 12 weeks of treatment was 86% (95% CI 84% to 88%) for statin-free patients and 54% (95% CI 46% to 61%) for statin-treated patients. Overall, 1003 subjects (80%; 95% CI 78% to 82%) achieved both lipid targets.

Conclusions: Algorithm-based statin dosing enables patients to achieve LDL-C and TC/HDL-C ratio targets quickly, with either no titration or a single titration.

4. **Comparative study of low doses of rosuvastatin and atorvastatin on lipid and glycemic control in patients with metabolic syndrome and hypercholesterolemia. Park JS, Kim YJ, Choi JY, Kim YN, Hong TJ, Kim DS, Kim KY, Jeong MH, Chae JK, Oh SK, Seong IW. Korean J Intern Med. 2010 Mar;25(1):27-35. Epub 2010 Feb 26.**

Abstract

Background/Aims: This multicenter, open-labeled, randomized trial was performed to compare the effects of rosuvastatin 10 mg and atorvastatin 10 mg on lipid and glycemic control in Korean patients with nondiabetic metabolic syndrome.

Methods: In total, 351 patients who met the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria for metabolic syndrome with low-density lipoprotein cholesterol (LDL-C) levels > or = 130 mg/dL were randomized to receive either rosuvastatin 10 mg (n = 173) or atorvastatin 10 mg (n = 178) for over 6 weeks.

Results: After 6 weeks of treatment, greater reductions in total cholesterol (- 35.94 +/- 11.38 vs. - 30.07 +/- 10.46%, p < 0.001), LDL-C (48.04 +/- 14.45 vs. 39.52 +/- 14.42%, p < 0.001), non-high-density lipoprotein cholesterol (- 42.93 +/- 13.15 vs. - 35.52 +/- 11.76%, p < 0.001), and apolipoprotein-B (- 38.7 +/- 18.85 vs. - 32.57 +/- 17.56%, p = 0.002) levels were observed in the rosuvastatin group as compared to the atorvastatin group. Overall, the percentage of patients attaining the NCEP ATP III goal was higher with rosuvastatin as compared to atorvastatin (87.64 vs. 69.88%, p < 0.001). Changes in glucose and insulin levels, and homeostasis model assessment of insulin resistance index were not significantly different between the two groups. The safety and tolerability of the two agents were similar.

Conclusions: Rosuvastatin 10 mg was more effective than atorvastatin 10 mg in achieving NCEP ATP III LDL-C goals in patients with nondiabetic metabolic syndrome, especially in those with lower NCEP ATP III target level goals.

5. **Comparison of effects of morning versus evening administration of ezetimibe/simvastatin on serum cholesterol in patients with primary hypercholesterolemia. Yoon HS, Kim SH, Kim JK, Ko SH, Ko JE, Park SJ, Park MG, Lee JH, Hyon MS. Ann Pharmacother. 2011 Sep;45(9):1172.**

Abstract

Background: Ezetimibe, a first-in-its-class inhibitor of cholesterol absorption, is an effective agent for combined use with statins to achieve low-density lipoprotein cholesterol (LDL-C) goals. Ezetimibe in combination with simvastatin as a single-tablet formulation has proven to be highly effective in reducing serum LDL-C through the dual inhibition of cholesterol absorption and biosynthesis. The effect of time of administration on efficacy of this combination therapy has not been evaluated.

Objective: To compare the effects of morning versus evening administration of ezetimibe/simvastatin on serum cholesterol levels of patients with primary hypercholesterolemia.

Methods: In this multicenter, open-label, randomized, 2-sequence, 2-period crossover study, patients with primary hypercholesterolemia randomly received ezetimibe/simvastatin 10 mg/20 mg once daily, either in the morning (within 1 hour of breakfast) or in the evening (within 1 hour of dinner) for 6 weeks.

Results: Data on 171 patients (87 in the morning administration group and 84 in the evening administration group) were analyzed. A significant reduction ($p \leq 0.001$) in the total cholesterol, triglyceride, high-density lipoprotein cholesterol, LDL-C, apo-lipoprotein B, and high-sensitivity C-reactive protein (hs-CRP) from baseline was achieved after each treatment. Noninferiority of morning administration versus evening administration was shown in the percentage reduction of the LDL-C level from baseline (difference, -1.62%; 90% CI -4.94 to 1.70). No significant difference was found between groups with respect to the percentage of changes in other lipid parameters from baseline. Furthermore, there was no significant difference in the percentage of change in hs-CRP as an antiinflammatory marker between the morning and evening administration groups. The frequency of adverse events was similar between groups.

Conclusions: Morning administration of ezetimibe/simvastatin 10 mg/20 mg is noninferior to evening administration with respect to LDL-C-lowering ability.

6. **Ezetimibe/simvastatin 10/20 mg versus simvastatin 40 mg in coronary heart disease patients. Averna M, Zaninelli A, Le Grazie C, Gensini GF. J Clin Lipidol. 2010 Jul-Aug;4(4):272-8. Epub 2010 Jun 1.**

Abstract

Background: Reducing low-density lipoprotein cholesterol (LDL-C) is the primary goal of therapy in patients with hypercholesterolemia and coronary heart disease (CHD).

Methods: This double blind placebo-controlled study enrolled patients 18 to 75 years of age with primary hypercholesterolemia and established CHD who were taking a stable daily dose of simvastatin 20 mg. Patients were randomized to ezetimibe/simvastatin 10/20 mg (eze/simva; n = 56) or simvastatin 40 mg (simva; n = 56) for 6 weeks. Percent change from baseline in LDL-C, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were assessed by use of the Student t test. The percent of patients achieving LDL-C less than 100 mg/dL (<2.6 mmol/L) or less than 80 mg/dL (<2.0 mmol/L) was analyzed via logistic regression with terms for treatment, baseline LDL-C, age, and gender.

Results: Baseline characteristics were similar between groups. Treatment with eze/simva combination resulted in significantly greater reductions in LDL-C, total cholesterol, and triglycerides versus doubling the dose of simva to 40 mg (all P < .01). Significantly more patients achieved LDL-C less than 100 mg/dL (<2.6 mmol/L) and less than 80 mg/dL (<2.0 mmol/L) with ezetimibe/simvastatin versus doubling the dose of simva to 40 mg (73.2% vs 25.0%; P < .001) for simvastatin. Changes in HDL-C were similar between treatments. Both treatments were generally well tolerated.

Conclusion: In high-risk CHD patients with hypercholesterolemia, treatment with eze/simva combination resulted in significantly greater reductions in LDL-C, total cholesterol and triglycerides, as well as greater achievement of recommended LDL-C targets, compared with doubling the simvastatin dose to 40 mg over the 6-week period. (Clinical trial registration number: NCT00423579).

7. **Fixed-dose combination fenofibrate/pravastatin 160/40 mg versus simvastatin 20 mg monotherapy in adults with type 2 diabetes and mixed hyperlipidemia uncontrolled with simvastatin 20 mg: a double-blind, randomized comparative study. Farnier M, Steinmetz A, Retterstøl K, Császár A. Clin Ther. 2011 Jan;33(1):1-12.**

Abstract

Background: Patients with type 2 diabetes mellitus and mixed hyperlipidemia have an increased cardiovascular risk and may not achieve recommended LDL-C and non-HDL-C goals on statin monotherapy. This study was designed to obtain regulatory approval of a fenofibrate/pravastatin 160/40 mg fixed-dose combination (FDC) capsule.

Objective: The aim of this study was to compare the efficacy and tolerability of this FDC and simvastatin 20 mg in patients with type 2 diabetes.

Methods: This multicenter, randomized, double-blind, parallel-arm study was conducted in patients with type 2 diabetes and mixed hyperlipidemia, without cardiovascular disease, and who were not at lipid goals with simvastatin 20 mg monotherapy. After a 6-week run-in period during which patients received simvastatin 20 mg, those with non-HDL-C concentrations ≥130 mg/dL or LDL-C concentrations ≥100 mg/dL and triglyceride concentrations 150 to 600 mg/dL were enrolled. Eligible patients were randomly assigned to receive 12-week treatment with fenofibrate/pravastatin 160/40 mg FDC or simvastatin 20 mg once daily, followed by a 12-week open-label tolerability-assessment period during which all patients received the FDC. The primary efficacy outcome was the mean percentage change in non-HDL-C after 12 weeks. Secondary efficacy outcomes included changes in other lipid and lipoprotein parameters, fibrinogen, and high-sensitivity C-reactive protein. Tolerability was assessed based on the prevalence of adverse events and abnormal laboratory data in each treatment group.

Results: A total of 291 patients were randomized to receive fenofibrate/pravastatin (n= 145) or simvastatin (n = 146). The mean (SD) age of the participants was 56.6 (8.9) years, 48.1% were men, and the body mass index was 31.3 (4.6) kg/m(2). The FDC was associated with a significantly greater reduction in non-HDL-C (primary end point) compared with simvastatin monotherapy (-12.9% [1.8] vs -6.8% [1.8]; P = 0.008). Triglyceride (-28.6% [3.7] vs +5.0% [3.6]; P < 0.001), fibrinogen (-11.5% [1.6] vs +0.3% [1.6]; P < 0.001), and HDL-C (+6.3% [1.3] vs +1.8% [1.3]; P = 0.008) concentrations also were significantly improved with the FDC compared with simvastatin monotherapy. The proportions of patients who achieved the LDL-C target (<100 mg/dL) were not significantly different between the 2 groups. The proportion of patients who achieved the combined end point of non-HDL-C <130 mg/dL and LDL-C <100 mg/dL was significantly greater with fenofibrate/pravastatin compared with simvastatin monotherapy (41 [28.5%] vs 26 [17.9%]; P < 0.05). The prevalences of patients who experienced ≥1 adverse event were not statistically different between the fenofibrate/pravastatin and simvastatin groups (17.2% vs 15.1%). However, compared with simvastatin monotherapy, the combination treatment was associated with significantly greater increases in alanine aminotransferase (+9.6% vs +1.5%; P = 0.03 between groups), creatinine (+13.7% vs +6.8%; P = 0.002 between groups), and homocysteine (+36.5% vs +1.6%; P < 0.001 between groups) concentrations.

Conclusions: In this selected population of adults with type 2 diabetes, the fenofibrate/pravastatin 160/40 mg FDC was associated with significantly greater changes from baseline in non-HDL-C, triglyceride, and HDL-C concentrations compared with simvastatin 20 mg. Both treatments were well tolerated.

8. **Safety and efficacy of ezetimibe added to atorvastatin versus up titration of atorvastatin to 40 mg in Patients > or = 65 years of age (from the ZETia in the ELDerly [ZETELD] study). Zieve F, Wenger NK, Ben-Yehuda O, Constance C, Bird S, Lee R, Hanson ME, Jones-Burton C, Tershakovec AM. Am J Cardiol. 2010 Mar 1;105(5):656-63. Epub 2009 Dec 24.**

Abstract

Few clinical studies have focused on the efficacy of lipid-lowering therapies in patients > or = 65 years of age. The percentage of change from baseline in low-density lipoprotein (LDL) cholesterol and the percentage of patients achieving prespecified LDL cholesterol levels after 12 weeks of ezetimibe 10 mg plus atorvastatin versus up titration of atorvastatin were assessed in subjects > or = 65 years old with hyperlipidemia and at high risk of coronary heart disease. After stabilization of atorvastatin 10-mg therapy, 1,053 patients, > or = 65 years old, at high risk of coronary heart disease, with and without atherosclerotic vascular disease and a LDL cholesterol level that was not <70 or <100 mg/dl, respectively, were randomized to receive ezetimibe added to atorvastatin 10 mg for 12 weeks versus up titration to atorvastatin 20 mg for 6 weeks followed by up titration to atorvastatin 40 mg for an additional 6 weeks. Ezetimibe added to

atorvastatin 10 mg resulted in significantly greater changes at week 6 in LDL cholesterol (p <0.001), significantly more patients with atherosclerotic vascular disease achieving a LDL cholesterol level of <70 mg/dl (p <0.001), and significantly more patients without atherosclerotic vascular disease achieving a LDL cholesterol level of <100 mg/dl (p <0.001) at weeks 6 and 12 compared to atorvastatin 20 mg or atorvastatin 40 mg. In addition, ezetimibe plus atorvastatin 10 mg resulted in significantly greater changes at week 6 in total cholesterol, triglycerides, non-high-density lipoprotein (HDL) cholesterol, apolipoprotein B (all p <0.001), and HDL cholesterol (p = 0.021) compared with atorvastatin 20 mg and significantly greater changes at week 12 in LDL cholesterol, non-HDL cholesterol, apolipoprotein A-I (p = 0.001), total cholesterol, apolipoprotein B (p <0.030), and HDL cholesterol (p <0.001) compared with atorvastatin 40 mg. Both treatments were generally well tolerated, with comparable safety profiles. In conclusion, adding ezetimibe to atorvastatin 10 mg produced significantly greater favorable changes in most lipids at 6 and 12 weeks and significantly greater attainment of prespecified LDL cholesterol levels than doubling or quadrupling the atorvastatin dose in patients > or =65 years old at high risk for coronary heart disease.

9. Safety and efficacy of ezetimibe/simvastatin combination versus atorvastatin alone in adults ≥65 years of age with hypercholesterolemia and with or at moderately high/high risk for coronary heart disease (the VYTELD study). Foody JM, Brown WV, Zieve F, Adewale AJ, Flaim D, Lowe RS, Jones-Burton C, Tershakovec AM. Am J Cardiol. 2010 Nov 1;106(9):1255-63.

Abstract

Higher than 80% of coronary heart disease-related mortality occurs in patients ≥65 years of age. Guidelines recommend low-density lipoprotein (LDL) cholesterol targets for these at-risk patients; however, few clinical studies have evaluated lipid-lowering strategies specifically in older adults. This multicenter, 12-week, randomized, double-blind, parallel-group trial evaluated the efficacy and safety of the usual starting dose of ezetimibe/simvastatin (10/20 mg) versus atorvastatin 10 or 20 mg and the next higher dose of ezetimibe/simvastatin (10/40 mg) versus atorvastatin 40 mg in 1,289 hypercholesterolemic patients ≥65 years of age with or without cardiovascular disease. Patients randomized to ezetimibe/simvastatin had greater percent decreases in LDL cholesterol (-54.2% for 10/20 mg vs -39.5% and -46.6% for atorvastatin 10 and 20 mg, respectively; -59.1% for 10/40 mg vs -50.8% for atorvastatin 40 mg; p <0.001 for all comparisons) and the number attaining LDL cholesterol <70 mg/dl (51.3% for 10/20 mg, 68.2% for 10/40 mg) and <100 mg/dl (83.6% for 10/20 mg; 90.3% for 10/40 mg) was significantly larger compared to those receiving atorvastatin for all prespecified dose comparisons (p <0.05 to <0.001). A significantly larger percentage of high-risk patients achieved LDL cholesterol <70 mg/dl on ezetimibe/simvastatin 10/20 mg (54.3%) versus atorvastatin 10 mg (10.9%, p <0.001) or 20 mg (28.9%, p <0.001) and ezetimibe/simvastatin 10/40 mg (69.2%) versus atorvastatin 40 mg (38.2%, p <0.001), and a significantly larger percentage of intermediate-risk patients achieved LDL cholesterol <100 mg/dl on ezetimibe/simvastatin 10/20 mg (82.1%) versus atorvastatin 10 mg (59.3%, p <0.05). Improvements in non-high-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and lipoprotein ratios were significantly greater with ezetimibe/simvastatin than atorvastatin for all comparisons (p <0.01 to <0.001). High-density lipoprotein cholesterol and triglyceride results were variable. All treatments were generally well tolerated. In conclusion, ezetimibe/simvastatin provided significantly greater improvements in key lipid parameters and higher attainment of LDL cholesterol targets than atorvastatin, with comparable tolerability.

10. **Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. Heart Protection Study Collaborative Group, Bulbulia R, Bowman L, Wallendszus K, Parish S, Armitage J, Peto R, Collins R. Lancet. 2011 Dec 10;378(9808):2013-20. Epub 2011 Nov 22.**

Abstract

Background: Findings of large randomised trials have shown that lowering LDL cholesterol with statins reduces vascular morbidity and mortality rapidly, but limited evidence exists about the long-term efficacy and safety of statin treatment. The aim of the extended follow-up of the Heart Protection Study (HPS) is to assess long-term efficacy and safety of lowering LDL cholesterol with statins, and here we report cause-specific mortality and major morbidity in the in-trial and post-trial periods.

Methods: 20,536 patients at high risk of vascular and non-vascular outcomes were allocated either 40 mg simvastatin daily or placebo, using minimised randomisation. Mean in-trial follow-up was 5·3 years (SD 1·2), and post-trial follow-up of surviving patients yielded a mean total duration of 11·0 years (SD 0·6). The primary outcome of the long-term follow-up of HPS was first post-randomisation major vascular event, and analysis was by intention to treat. This trial is registered with ISRCTN, number 48489393.

Findings: During the in-trial period, allocation to simvastatin yielded an average reduction in LDL cholesterol of 1·0 mmol/L and a proportional decrease in major vascular events of 23% (95% CI 19-28; p<0·0001), with significant divergence each year after the first. During the post-trial period (when statin use and lipid concentrations were similar in both groups), no further significant reductions were noted in either major vascular events (risk ratio [RR] 0·95 [0·89-1·02]) or vascular mortality (0·98 [0·90-1·07]). During the combined in-trial and post-trial periods, no significant differences were recorded in cancer incidence at all sites (0·98 [0·92-1·05]) or any particular site, or in mortality attributed to cancer (1·01 [0·92-1·11]) or to non-vascular causes (0·96 [0·89-1·03]).

Interpretation: More prolonged LDL-lowering statin treatment produces larger absolute reductions in vascular events. Moreover, even after study treatment stopped in HPS, benefits persisted for at least 5 years without any evidence of emerging hazards. These findings provide further support for the prompt initiation and long-term continuation of statin treatment.

11. **Incremental cholesterol reduction with ezetimibe/simvastatin, atorvastatin and rosuvastatin in UK General Practice (IN-PRACTICE): randomised controlled trial of achievement of Joint British Societies (JBS-2) cholesterol targets. McCormack T, Harvey P, Gaunt R, Allgar V, Chipperfield R, Robinson P; IN-PRACTICE study. Int J Clin Pract. 2010 Jul;64(8):1052-61. Epub 2010 May 12.**

Abstract

Aim: The aim of this study was to compare ezetimibe/simvastatin combination therapy with intensified statin monotherapy as alternative treatment strategies to achieve the Joint British Societies (JBS)-2 and National Institute for Health and Clinical Excellence low-density-lipoprotein cholesterol (LDL-C) target of < 2 mmol/l for secondary prevention or JBS-2 LDL-C target of < 2 mmol/l for primary prevention in high-risk patients who have failed to reach target with simvastatin 40 mg.

Methods: This is a prospective, double-blind study conducted in 34 UK primary care centres; 1748 patients with established cardiovascular disease (CVD), diabetes or high risk of CVD who had been taking simvastatin 40 mg for > or = 6 weeks were screened and 786 (45%) with fasting LDL-C > or = 2.0 mmol/l (and < 4.2 mmol/l) at screening and after a further 6-week run-in period on simvastatin 40 mg were randomised to ezetimibe/simvastatin 10/40 mg (as a combination tablet; n = 261), atorvastatin 40 mg (n = 263) or rosuvastatin 5 mg (n = 73) or 10 mg (n = 189) once daily for 6 weeks. Rosuvastatin dose was based on UK prescribing instructions. The primary outcome measure was the proportion of patients achieving LDL-C < 2 mmol/l at the end of the study.

Results: The percentage of patients (adjusted for baseline differences) achieving LDL-C < 2 mmol/l was 69.4% with ezetimibe/simvastatin 10/40 mg, compared with 33.5% for atorvastatin 40 mg [odds ratio 4.5 (95% CI: 3.0-6.8); p < 0.001] and 14.3% for rosuvastatin 5 or 10 mg [odds ratio 13.6 (95% CI: 8.6-21.6); p < 0.001]. Similar results were observed for achievement of total cholesterol < 4.0 mmol/l. All study treatments were well tolerated.

Conclusion: Approximately 45% of patients screened had not achieved LDL-C < 2 mmol/l after > or = 12 weeks of treatment with simvastatin 40 mg. In this group, treatment with ezetimibe/simvastatin 10/40 mg achieved target LDL-C levels in a significantly higher proportion of patients during a 6-week period than switching to either atorvastatin 40 mg or rosuvastatin 5-10 mg.

12. **Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, Armitage J, Bowman L, Wallendszus K, Bulbulia R, Rahimi K, Haynes R, Parish S, Peto R, Collins R. Lancet. 2010 Nov 13;376(9753):1658-69. Epub 2010 Nov 8.**

Abstract

Background: Lowering of LDL cholesterol reduces major vascular events, but whether more intensive therapy safely produces extra benefits is uncertain. We aimed to establish efficacy and safety of more intensive statin treatment in patients at high cardiovascular risk.

Methods: We undertook a double-blind randomised trial in 12,064 men and women aged 18-80 years with a history of myocardial infarction. Participants were either currently on or had clear indication for statin therapy, and had a total cholesterol concentration of at least 3·5 mmol/L if already on a statin or 4·5 mmol/L if not. Randomisation to either 80 mg or 20 mg simvastatin daily was done centrally using a minimisation algorithm. Participants were assessed at 2, 4, 8, and 12 months after randomisation and then every 6 months until final follow-up. The primary endpoint was major vascular events, defined as coronary death, myocardial infarction, stroke, or arterial revascularisation. Analysis was by intention to treat. This study is registered, number ISRCTN74348595.

Findings: 6031 participants were allocated 80 mg simvastatin daily, and 6033 allocated 20 mg simvastatin daily. During a mean follow-up of 6·7 (SD 1·5) years, allocation to 80 mg simvastatin produced an average 0·35 (SE 0·01) mmol/L greater reduction in LDL cholesterol compared with allocation to 20 mg. Major vascular events occurred in 1477 (24·5%) participants allocated 80 mg simvastatin versus 1553 (25·7%) of those allocated 20 mg, corresponding to a 6% proportional reduction (risk ratio 0·94, 95% CI 0·88-1·01; p=0·10). There were no apparent differences in numbers of haemorrhagic strokes (24 [0·4%] vs 25 [0·4%]) or deaths attributed to vascular (565 [9·4%] vs 572 [9·5%]) or non-vascular (399 [6·6%] vs 398 [6·6%]) causes. Compared with two (0·03%) cases of myopathy in patients taking 20 mg simvastatin daily, there were 53 (0·9%) cases in the 80 mg group.

Interpretation: The 6% (SE 3·5%) reduction in major vascular events with a further 0·35 mmol/L reduction in LDL cholesterol in our trial is consistent with previous trials. Myopathy was increased with 80 mg simvastatin daily, but intensive lowering of LDL cholesterol can be achieved safely with other regimens.