Drug Class Review

HMG-CoA Reductase Inhibitors (Statins) and Fixed-Dose Combination Products Containing a Statin

Expanded Scan Report

April 2017

Last Report: Update #5, November 2009

Last Preliminary Update Scan: Scan #5, March 2017

Last Expanded Scan: January 2016

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OBJECTIVE

The purpose of this expanded version of a preliminary updated literature scan process is to provide a preview of the volume and nature of new research that has emerged subsequent to the previous full review, with some additional features to allow more insight into the potential impact of the new evidence. This expanded scan builds on prior preliminary update scans and the prior expanded scan. The expanded scan includes quality assessment of key trials that would fill a gap in evidence in the last full report update, with presentation of key results, and the study authors' conclusions. Comprehensive review and synthesis of the new research presented in this report along with previous evidence is not included, and would follow only if a full update of the report were commissioned. The literature search for this report focuses only on new randomized controlled trials, comparative effectiveness reviews, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Reports

Single Drug Addendum: Pitavastatin, June 2013
Update #5, November 2009 (searches through June 2009)
Update #4, August 2006
Update #3, September 2005
Update #2, March 2004
Update #1, July 2003
Original Report, April 2002

Dates of Previous Scan Reports

Scan #5, March 2017
Expanded Scan, January 2016
Scan #4, April 2015
Scan #3, August 2014
Scan #2, August 2013
Scan #1, March 2011

Scope and Key Questions

1. How do statins and fixed-dose combination products containing a statin and another lipid lowering drug compare in their ability to reduce LDL-C?
    a. Are there doses for each statin or fixed-dose combination product containing a statin and another lipid lowering drug that produce similar percent reduction in LDL-C between statins?
    b. Is there a difference in the ability of a statin or fixed-dose combination product containing a statin and another lipid lowering drug to achieve National Cholesterol Education Panel goals?

2. How do statins and fixed-dose combination products containing a statin and another lipid lowering drug compare in their ability to raise HDL-C?

   a. Are there doses for each statin or fixed-dose combination product containing a statin and another lipid lowering drug that produce similar percent increase in HDL-C between statins?
   b. Is there a difference in the ability of a statin or fixed-dose combination product containing a statin and another lipid lowering drug to achieve National Cholesterol Education Panel goals?

3. How do statins and fixed-dose combination products containing a statin and another lipid lowering drug compare in their ability to reduce the risk of nonfatal myocardial infarction, coronary heart disease (angina), coronary heart disease mortality, all-cause mortality, stroke, hospitalization for unstable angina, or need for revascularization (coronary artery bypass graft, angioplasty, or stenting)?

4. Are there differences in effectiveness of statins and fixed-dose combination products containing a statin and another lipid lowering drug in different demographic groups or in patients with comorbid conditions (e.g., diabetes, obesity)?

5. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid lowering drug when used in the general population of children or adults?

6. Are there differences in the harms of statins or fixed-dose combination products containing a statin and another lipid lowering drug when used in special populations or with other medications (drug-drug interactions)? In addressing this question, we will focus on the following populations:
   a. Patients with HIV
   b. Organ transplant recipients
   c. Patients at high risk for myotoxicity (e.g., patients with a history of statin-associated muscle-related harms due to drug-drug/drug-food interactions, patients co-administered fibrates, patients taking potent 3A4 inhibitors, elderly patients, especially elderly females)
   d. Patients at high risk for hepatotoxicity
   e. Patients using fibrates (gemfibrozil, fenofibrate, fenofibric acid) or niacin
   f. Children with nephrotic syndrome

INCLUSION CRITERIA

Populations

- Outpatients targeted for primary or secondary prevention of coronary heart disease or non-coronary forms of atherosclerotic disease with or without hypercholesterolemia.
- Inpatients with acute coronary syndrome or undergoing revascularization (if the statin was continued after hospital discharge and if health outcomes were reported).
- Familial hypercholesterolemia (homozygous or heterozygous)
- Both children and adults will be included.

- *Exclusions:* adults with rare, severe forms of hypercholesterolemia (LDL-C ≥ 250mg/dL).

Interventions

Table 1. Individual statins

Active ingredient	Brand name	Approval date	Approved dose range (mg/d)
Atorvastatin	Lipitor	12/17/1996	10 to 80
Fluvastatin	Lescol	12/31/1993	20 to 80
Fluvastatin extended release	Lescol XL	10/06/2000	20 to 80
Lovastatin	Generic	08/31/1987	10 to 80
Lovastatin extended release	Altoprev	06/26/2002	20 to 60
Pitavastatin	Livalo	08/03/2009	1 to 4
Pravastatin	Pravachol	10/31/1991	40 to 80
Rosuvastatin	Crestor	08/12/2003	5 to 40
Simvastatin	Zocor	12/23/1991	5 to 40

Shading indicates drugs approved since the 2009 update report.

Table 2. Fixed-dose combination products containing a statin

Active ingredients	Brand name	Approval date	Approved dose range (mg/d)
Atorvastatin; ezetimibe	Liptruzet	05/03/2013 (discontinued 2015)	10/10 to 80/10
Lovastatin; niacin extended release	Advicor	12/17/2001 (Approval withdrawn 2016)	NA
Simvastatin; ezetimibe	Vytorin	07/23/2004	10/10 to 40/10
Simvastatin; niacin extended release	Simcor	2/15/2008 (Approval withdrawn 2016)	NA

Shading indicates drugs approved since the 2009 update report.

Comparators: Effectiveness and harms of individual statins

- For Key Questions 1 and 2, head-to-head trials comparing one statin to another.
- For other key questions, trials comparing a statin to placebo.

Comparators: Effectiveness and harms of fixed-dose combination products containing a statin

- Head-to-head trials comparing one fixed-dose combination product to another.
- Trials comparing a fixed-dose combination product to an individual statin or placebo.
- *Exclusions:* Trials comparing a fixed-dose combination product to the product's individual components given separately (co-administration).

Effectiveness outcomes

- Reduction in nonfatal MI, CHD, mortality (CHD and all-cause), stroke, and need for revascularization (coronary artery bypass grafting, angioplasty and coronary stents)
- LDL-C lowering ability
- HDL-C raising ability

Harms outcomes

- Overall adverse events
- Withdrawals due to adverse events
- Serious adverse events
- Specific adverse events (including, but not limited to, hepatotoxicity, myopathy, rhabdomyolysis, renal toxicity, myalgia)

Study designs

- For assessment of both effectiveness and harms, randomized controlled trials and systematic reviews.

Study duration

- All studies must be ≥12 weeks in duration (scope limit added for Scan #5)

METHODS FOR EXPANDED SCAN

In consultation with representatives from the participating organizations of DERP, methods and scope for an expanded version of a scan of studies published since the last report or preliminary update scan were developed. The expanded scan focuses on evidence for new drugs and drugs with little or no evidence in the prior report. Emphasis is placed on head-to-head evidence and health outcomes.

Literature Searches

To identify relevant citations, we searched Ovid MEDLINE® and Ovid MEDLINE® In-Process & Other Non-Indexed Citations January 2016 through March 2017 using terms for included drugs. We limited results to randomized controlled trials and controlled clinical trials conducted in humans and published in English. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm - "Our Publications" and "Our Databases"). All citations were imported into an electronic database (EndNote X7) and duplicate citations were removed.

We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm and http://www.accessdata.fda.gov/scripts/cder/drugsatfda/) for identification of new drugs and new serious harms (e.g. boxed warnings). To identify new drugs, we also searched CenterWatch (http://www.centerwatch.com), a privately-owned database of clinical trials information, and conducted a limited internet search.

Study Selection

We first selected all trials that appeared to meet inclusion criteria for this report, as per usual DERP procedures for a preliminary update scan. We provided an accounting of all potentially eligible studies published since the last full report update.

From this set of trials, we then selected a subset for full-text review, data abstraction and quality assessment, focusing on evidence for drugs not included in the 2009 update report. (We also excluded trials included in the 2013 single-drug addendum on pitavastatin.) We prioritized primary publications of head-to-head randomized controlled trials, but for populations without head-to-head evidence we included placebo-controlled trials. Secondary publications (e.g. subgroup analyses) were screened to identify any that resulted in strongly differing results compared to the overall trial; any such publications are noted, with abstracts available on request. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

Quality Assessment

For those studies meeting the criteria for full-text review and data abstraction (above), a single reviewer assessed the quality of primary randomized controlled trials using the DERP methodology, resulting in ratings of good, fair or poor. Any study rated poor quality was reviewed by a second reviewer, and any differences in judgment resolved through consensus.

Data Abstraction

For trials selected for additional assessment that were rated fair or good quality, we abstracted study identifiers (author, year, study name), study quality, and study/patient characteristics (duration, number of participants, mean age). We compared the dose of each drug to FDA-approved dose ranges (reported in Tables 1 and 2), and noted where doses were outside of the approved range, or at the low or high end of this range. We included two key benefit outcomes and two key harms outcomes determined a priori by discussion among the team. These were:

Benefit outcomes

1. Cardiovascular event outcomes, including mortality
2. All-cause mortality

If these were not reported as primary outcomes we included

1. LDL-C
2. HDL-C

Harms outcomes

1. Withdrawals due to adverse events
2. Overall adverse events
3. Muscle pain (myalgia)

We also abstracted the author's conclusion statements regarding benefit and/or harms outcomes.

RESULTS

New Drugs

Identified since the last update report

New Drugs

Pitavastatin (Livalo®) was FDA approved in August 2009 as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, and triglycerides, and to increase high-density lipoprotein cholesterol.

New Formulations

Simvastatin oral suspension: approved on 4/21/2016 in 20 mg/5mL and 40 mg/5mL doses.

Discontinued Drugs

Evidence for the following drugs not included in this scan report

Atorvastatin/ezetimibe (Liptruzet®): the FDA approved a new fixed dose combination product comprised of atorvastatin and ezetimibe on 5/3/2013 for the treatment of hyperlipidemia. However, all Liptruzet lots were recalled in January 2014 for a packaging problem, and in June 2015 Merck notified the FDA that they were withdrawing Liptruzet from the market. This decision was not due to safety or efficacy concerns.[1]

Lovastatin/niacin (Advicor®) and simvastatin/niacin (Simcor®): these two combination products of statins and niacin were approved in 2001 and 2008, respectively. On 4/18/2016, the FDA withdrew approval of both drugs based on evidence from cardiovascular outcome trials that led the FDA to conclude that their benefits no longer outweighed their harms.[2]

New Serious Harms (Boxed Warnings)

Identified since the last update report

No new boxed warnings.

New Comparative Effectiveness Reviews

Identified since the last update report

Since the last full update report, we have identified 2 potentially relevant comparative effectiveness reviews published within the last 3 years. Abstracts and citations for both reviews are available on request. One review is a 2014 AHRQ Evidence-based Practice Center report on combination therapy compared with intensification of statin therapy. The second review is a 2016 U.S. Preventive Services Task Force review on statin use for the prevention of cardiovascular disease in adults. However, neither review was able to answer key questions

[1] https://www.federalregister.gov/documents/2015/11/20/2015-29639/determination-that-liptruzet-ezetimibe-and-atorvastatin-tablets-10-milligrams10-milligrams-10

[2]https://www.federalregister.gov/documents/2016/04/18/2016-08894/abbvie-inc-withdrawal-of-approval-of-new-drug-applications-for-advicor-and-simcor

posed by the DERP report, because each pooled results across statins rather than comparing results for individual statins. The 2016 USPSTF report pools across all included statins, while the 2014 AHRQ report classifies statins by potency, then compares lower-potency statin given with ezetimibe to higher-potency statin alone. Because no results for individual statins were reported, we did not summarize findings of these reviews for this expanded scan report.

Randomized Controlled Trials

Identified since the last update report

Medline searches for this expanded scan report resulted in 639 citations, of which 7 new head-to-head trials and 2 secondary analyses of head-to-head trials were determined to be eligible. Cumulatively, including trials identified in prior scans and the prior expanded scan, a total of 46 primary head-to-head trials, 16 secondary analyses of head-to-head trials, and 57 placebo-controlled trials are eligible for inclusion in a full report update. Table 3 shows the 3 trials reporting cardiovascular event outcomes as primary outcomes, and Table 4 shows the 43 trials reporting only lipid outcomes. There were 2 new trials of older statins (those included in the last report). Bando 2016 had findings similar to those in the 2009 report for atorvastatin and rosuvastatin. Izawa 2015 reported clinical outcomes for pravastatin compared with atorvastatin, which were not previously available, but found no statistically significant difference in these outcomes between drugs. Abstracts of studies are available upon request.

Table 3. New head-to-head trials of statins reporting cardiovascular/long-term outcomes (N=3, cumulative since last report update)

Author Year	Comparison	Population	Outcome
de Zeeuw 2015	Atorvastatin vs rosuvastatin	Patients with progressive renal disease	Harms only (renal effects)
Izawa 2015	Pravastatin vs atorvastatin	Acute myocardial infarction	Composite of all-cause death, non-fatal MI, non-fatal stroke, unstable angina or CHF requiring hospital admission, or any type of coronary revascularization
Sardella 2013	Atorvastatin vs rosuvastatin	Patients with stable angina undergoing elective PCI	Occurrence of major cardiac and cerebrovascular events

Abbreviations: ACS, acute coronary syndrome; PCI, percutaneous coronary intervention
Shading indicates trials identified in the present scan

Table 4. New head-to-head trials of statins reporting lipid outcomes (N=43, cumulative since last report update)

Author Year	Comparison	Population
Abe 2015	Pitavastatin vs rosuvastatin	Dyslipidemic patients with chronic kidney disease
Araujo 2010	Simvastatin vs simvastatin + ezetimibe	Hypercholesterolemia
Bando 2016	Atorvastatin vs. rosuvastatin	Japanese patients with hypercholesterolemia
Eriksson 2011	Pitavastatin vs simvastatin	Primary hypercholesterolemia/dyslipidemia + >2 CHD risk factors
Florentin 2011	Simvastatin vs simvastatin/ezetimibe	1° hypercholesterolemia
Foody 2010	Ezetimibe/simvastatin vs atorvastatin	Hypercholesterolemia, ≥ 65 years ± CVD
Gumprecht 2011	Pitavastatin vs atorvastatin	Type 2 DM and dyslipidemia
Hall 2009	Rosuvastatin vs simvastatin	Hyperlipidemia
Han 2012	Pitavastatin vs atorvastatin	Hypercholesterolemia + elevated ALT
Hongo 2011	Rosuvastatin vs fluvastatin	Japanese patients with dyslipidemia
Ishigaki 2014	Pitavastatin vs pravastatin	Hypercholesterolemic subjects with type 2 diabetes
Kasmas 2012	Rosuvastatin vs simvastatin/ezetimibe	NR
Koksal 2011	Atorvastatin vs rosuvastatin	Type 2 DM with LDL-C > 100 mg/dl
Kurogi 2013	Pitavastatin vs atorvastatin	Stable CAD, hypercholesterolemia, low HDL
Lablanche 2010	Rosuvastatin vs atorvastatin	Acute coronary syndrome
Lee 2013	Ezetimibe/simvastatin vs atorvastatin	Type 2 DM and LDL-C > 100 mg/dl
Lee 2014	Pitavastatin vs pravastatin	Ischemic CHF
Liu 2013	Pitavastatin vs atorvastatin	Ethnic Chinese patients with hypercholesterolemia
Matsushita 2016	Atorvastatin vs pitavastatin vs pravastatin vs fluvastatin	Acute coronary syndrome
Masuda 2015	Rosuvastatin + ezetimibe vs. rosuvastatin	Stable CAD requiring PCI
Moreira 2014	Rosuvastatin vs ezetimibe/simvastatin	Hyperlipidemia
Moutzouri 2013	Simvastatin/ezetimibe vs simvastatin vs rosuvastatin	Dyslipidemia
Murrow 2012	Pravastatin vs atorvastatin	Hyperlipidemia + metabolic syndrome/DM
Nicholls 2011	Atorvastatin vs rosuvastatin	CHD
Nohara 2012	Rosuvastatin vs pravastatin	Hypercholesterol + thick carotid intima-media
Ogawa 2014	Rosuvastatin vs atorvastatin	Hypercholesterol + DM
Ose 2009	Pitavastatin vs simvastatin	Primary hypercholesteremia/dyslipidemia
Ramos 2011	Rosuvastatin vs simvastatin + ezetimibe	Primary hypercholesterolemia
Rosen 2013	Ezetimibe/simvastatin vs simvastatin or atorvastatin vs rosuvastatin	Cardiovascular disease + DM
Saku 2011	Atorvastatin vs rosuvastatin vs pitavastatin	Risk factors for CAD and elevated LDL-C
Sasaki 2013	Pravastatin vs atorvastatin	Men > 20 years; postmenopausal women
Scheffer 2013	Atorvastatin vs simvastatin	DM and/or obesity and/or hypertension
Shimabukuro 2011	Pitavastatin vs atorvastatin	DM with hypercholesterolemia/triglyceridemia
Shioji 2014	Atorvastatin vs rosuvastatin	Patients with DM at risk of CAD
Sponseller 2014	Pitavastatin vs pravastatin	Primary hyperlipidemia or mixed dyslipidemia
Stender 2013	Pitavastatin vs pravastatin	Elderly with hypercholesterol/dyslipidemia
Tani 2015	Pitavastatin vs atorvastatin	Hypercholesterolemia
Toyama 2011	Rosuvastatin vs atorvastatin	CAD
Watanabe 2015	Pitavastatin vs pravastatin	Patients with atherosclerotic plaque

Author Year	Comparison	Population
West 2011	Simvastatin vs simvastatin + ezetimibe	Peripheral arterial disease
Yamamoto 2014	Pravastatin vs rosuvastatin	Placement of drug-eluting stent
Yanagi 2011	Rosuvastatin vs pitavastatin	DM with hyperlipidemia
Yoshida 2013	Pitavastatin vs atorvastatin	Hypercholesterolemia

Abbreviations: CAD, coronary artery disease; CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; DM, diabetes mellitus; MI, myocardial infarction; NR, not reported; PCI, percutaneous coronary intervention
Shading indicates trials identified in the present scan

Of the 46 included head-to-head trials, 18 were of pitavastatin, approved since the last full report. Since the last expanded scan on this topic (January 2016), there are 5 new head-to-head trials of pitavastatin. We have identified no new trials of the new simvastatin formulation published since the last expanded scan.

We excluded from additional assessment trials included in the 2013 Single Drug Addendum for pitavastatin, and conducted quality assessment on the remaining 10 trials. Two of these trials were rated good quality and 6 were rated fair quality and met criteria for further reporting in this expanded scan. The remaining 2 poor-quality studies were excluded from further reporting. See Appendix A for quality assessments. Table 5 below provides the study characteristics for fair and good quality trials, key results and the trial author's conclusions in brief.

For the 8 pitavastatin studies, the sample sizes ranged from 42 to 328; treatment duration was 12 weeks for 3 studies, 6 to 36 months for the other 5. Table 5 also shows the tested doses of included drugs, with comparisons to FDA-approved dose ranges (reported in Tables 1 and 2). In all 8 studies, the tested dose of pitavastatin was higher than that of comparators, for example with a pitavastatin dose in the middle of the range and comparator at the lower end (e.g. Liu, 2013), or pitavastatin at the high end of the dose range and the comparator in the middle (e.g. comparisons to atorvastatin and fluvastatin in Matsushita, 2016).

None of the pitavastatin studies reported cardiovascular events or mortality outcomes. For lipid outcomes, authors conclude that pitavastatin improved lipid profiles to a greater degree than pravastatin, but pitavastatin doses were higher; in the SAPHIRE trial, the pravastatin dose was below the FDA-recommended range, while pitavastatin was at the high end of the range. Authors found no differences in effects on LDL or HDL between pitavastatin and atorvastatin; again the pitavastatin dose was higher, though the discrepancy was less than for pravastatin. All 3 studies gave moderate doses of pitavastatin compared with atorvastatin at a low, but approved, dose. One study found low-dose rosuvastatin to be more effective than pitavastatin in lowering LDL and raising HDL. Another trial compared pitavastatin to 3 other statins, but doses were again not comparable and results thus difficult to interpret. Adverse events were either not reported or occurred in few participants, and so were difficult to compare across drugs. One study reported overall adverse events, with similar rates for pitavastatin and pravastatin.

Table 5. New good- or fair-quality randomized controlled trials of pitavastatin (N=8)

Author, Year Trial Name Quality Rating	Drug and Dose Comparison Population	N Duration Mean Age	Benefit Outcomes	Harms Outcomes	Author's Conclusions
Abe, 2015 Fair	Pitavastatin 1 or 2 mg Rosuvastatin **2.5*** mg Dyslipidemia & chronic kidney disease	134 12 months 69.7 years	Pitavastatin vs. Rosuvastatin Percent change from baseline to 12 months, % (SD): LDL-C: -33.9 (14.2) vs. -41.1 (15.2), P=0.0058 HDL-C: -3.6 (16.2) vs. 3.8 (17.8), P=0.0131	WAE: NR Overall AE: NR Myalgia: NR	"The study results indicate that rosuvastatin 2.5 mg is superior to pitavastatin 1 mg and 2 mg in terms of the lipid lowering effectiveness without adverse effects on renal function in dyslipidemic patients with concurrent CKD."
Ishigaki, 2014 Fair	Pitavastatin 1-2 mg Pravastatin **10 mg*** Hypercholesterolemia & Type 2 diabetes	97 36 months 59.5 years	Pitavastatin vs. Pravastatin LDL-C (% change): -37.2 vs. -25.0, P < 0.001 HDL-C (% change): 5.7 vs. 4.5, P = 0.74	WAE: NR Overall AE: NR Myalgia n (%): 1 (2) vs. 2 (3%)	"The LDL-C decreased significantly…at the 36 month follow-up in the pitavastatin group and …in the pravastatin group. The between-group difference in these decreases was highly significant. (P<0.01)…The HDL-C levels increased significantly …in the pitavastatin treatment but not in the pravastatin treatment…"
Lee, 2014 SAPHIRE Fair	Pitavastatin **4 mg*** Pravastatin **10 mg*** Ischemic congestive heart failure	69 52 weeks 64.4 years	Pitavastatin vs. Pravastatin Change (52 week-baseline)/baseline, p-value: LDL-C: -30.33 vs. -12.39, P = 0.003 HDL-C: 9.36 vs. 0.89, P = 0.659	WAE: NR Overall AE: NR Myalgia: "No treatment-related AEs were found in either group by the investigators."	"The reduction in LDL-C in the pitavastatin group was significantly greater than the 12% reduction in the 10 mg pravastatin group (p=0.003)… The HDL cholesterol level was increased by 9% in the 4 mg pitavastatin group with borderline significance (p=0.052); however, no change was observed in the pravastatin group (p=0.635)."
Liu, 2013 PAPAGO-T Good	Pitavastatin 2 mg Atorvastatin **10 mg**** Hypercholesterolemia ± diabetes	225 12 weeks 58.7 years	Pitavastatin vs. Atorvastatin Percentage change from baseline to week 12: LDL-C: -35.0 vs. -38.4, between-group P = NS HDL-C: -1.7 vs. -1.8, between-group P = NS	WAE: NR Overall AE: NR Myalgia n (%): 1 (0.9) vs. 2 (1.8)	"Both pitavastatin (2 mg/day) and atorvastatin (10 mg/day) were well tolerated, lowered LDL-C, and improved the lipid profile to a comparable degree in high-risk Taiwanese patients with hypercholesterolemia."
Matsushita, 2016 YOKOHAMA-ACS Fair for	Pitavastatin **4 mg***** (M) Atorvastatin 20 mg (M) Fluvastatin 30 mg (L) Pravastatin **10 mg*** (L) M: described as	102 10 months 62.8 years	Pitavastatin vs. Atorvastatin vs. Fluvastatin vs. Pravastatin Percent change baseline to 10 months: LDL-C: -48 vs. -43 vs. -28 vs. -24, P < 0.001	*Poor quality for harms, outcomes not abstracted*	"..moderate-intensity statins induced greater reduction in LDL-C compared with low-intensity statins (-45% vs. 25%, P < 0.001)…atorvastatin, but not the other 3 statins, significantly

Author, Year Trial Name Quality Rating	Drug and Dose Comparison Population	N Duration Mean Age	Benefit Outcomes	Harms Outcomes	Author's Conclusions
cholesterol, poor for harms	moderate-intensity L: low-intensity ACS with PCI		HDL-C: 10 vs. 1 vs 8 vs 7, P = 0.36		increased high-density lipoprotein cholesterol (HDL-C)..”
Sponseller, 2014 NCT01256476 Good	Pitavastatin **4 mg***** Pravastatin **40 mg**** Dyslipidemia	328 12 weeks 57.9 years	Pitavastatin vs. Pravastatin Median percent change from baseline to week 12: LDL-C: -38.1 vs. -26.4, difference -12.5 (P<0.001) HDL-C: 6.3 vs. 5.2, difference 1.3 (P=0.101)	WAE, n (%): 2 (1.2) vs. 1 (0.6) Overall AE, n (%): 78 (47.6) vs. 73 (44.5) Myalgia, n (%): 3 (1.8) vs. 4 (2.4)	“Pitavastatin 4 mg demonstrated superior LDL-C reductions compared with pravastatin 40 mg after 12 weeks of therapy in adults with primary hyperlipidemia or mixed (combined) dyslipidemia. There were no new safety findings in the trial.”
Tani, 2014	Pitavastatin 2 mg Atorvastatin **10 mg**** Hypercholesterolemia	108 6 months 59.9 years	Pitavastatin vs. Atorvastatin LDL-C, % change: -36.8 vs. -36.6, P = 0.89 HDL-C, % change: 0.43 vs. 2.7, P = 0.35	WAE: NR Overall AE: NR Myalgia: NR	“There were no significant differences between the two groups in the changes in the low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C)…”
Yoshida, 2013 VISION Fair	Pitavastatin 2 mg Atorvastatin **10 mg**** Hyperlipidemia	42 12 weeks 60.6 years	Pitavastatin vs. Atorvastatin LDL-C, % change: -42.8 vs. -44.1, P = NS HDL-C, % change: 9.2 vs. 3.8, P = NS	WAE: NR Overall AE: NR Myalgia: NR	“Pitavastatin and atorvastatin significantly decreased LDL-C…and there were no significant differences in the mean % change between statins…Pitavastatin significantly increased HDL…whereas atorvastatin did not change (HDL), but the difference …(was) not significant between groups.”

Comments on doses in **bold:**
*Below FDA-approved dose range shown on drug label
**Lower end of FDA-approved dose range shown on drug label
***Upper end of FDA-approved dose range shown on drug label
Abbreviations: AE, adverse event; CKD, chronic kidney disease; HCL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WAE, withdrawal due to adverse events.
[a]Primary efficacy endpoint: composite of death from cardiovascular disease, a major coronary event (nonfatal myocardial infarction, unstable angina requiring hospitalization, coronary revascularization ≥ 30 days after randomization), or nonfatal stroke.
Shading indicates trials identified in the present scan

Secondary Publications

There are a total of 16 secondary publications related to studies already included in the full report or identified in a scan; these are summarized in Table 6. Of these, 2 were new in this scan, and both were secondary analyses of the IMPROVE-IT trial. Results from these trials did not differ substantially from the overall study results.

Table 6. Secondary analysis publications for trials included in the prior report or scans

Comparison	# (Name)	Focus of analysis
Atorvastatin vs. simvastatin	4 (IDEAL)	CV events in population subgroups (1), longer-term outcomes (1), Lipids in population subgroups (2)
Atorvastatin vs. pravastatin	2 (PROVE-IT-TIMI 22) 2 (PROVE-IT)	Adverse events, CV events in population subgroups
Atorvastatin vs. rosuvastatin	2 (SATURN) 1 (ARTMAP) 1 (LUNAR)	Lipids in population subgroups
Simvastatin/ezetimibe vs. simvastatin	2 (IMPROVE-IT)	CV death, MI, stroke, unstable angina leading to hospitalization, coronary revascularization, LDL-C
Pravastatin vs. rosuvastatin	1 (JART)	Population subgroup (thickened carotid intima-media)
Simvastatin/ezetimibe vs. simvastatin or atorvastatin vs. rosuvastatin	1	Lipids in Diabetics ± metabolic syndrome

Shading indicates trials identified in the present scan

Placebo-controlled Trials

Since the last update report, we have identified 57 placebo-controlled trial publications that are potentially relevant to this topic. These trials relate primarily to specific population subgroups.

SUMMARY

Two new drugs have been approved since the last report update, but one (atorvastatin/ezetimibe) has since been discontinued; pitavastatin is the one new drug still marketed in the U.S. Two fixed-dose combination products of a statin with niacin were also discontinued. There were no new boxed warnings, and the 2 new comparative effectiveness reviews did not report results for individual statins. Since the last report update in 2009, we have identified a total of 46 head-to-head trials, 16 secondary analyses of head-to-head trials, and 57 placebo-controlled trials (including 2 in children) that would be eligible for inclusion in a report update.

Eighteen head-to-head trials of the new drug pitavastatin were identified, with 8 of these rated either fair or good quality. In 3 head-to-head studies, trial authors concluded that pitavastatin improved lipid profiles to a greater degree than pravastatin; however pitavastatin doses were substantially higher than those of pravastatin. Study authors reported no differences in changes in LDL or HDL between treatment with pitavastatin and treatment with atorvastatin in 3 head-to-head trials, though pitavastatin doses were somewhat higher than atorvastatin doses. One study showed low-dose rosuvastatin to be more effective than pitavastatin in lowering LDL and raising HDL. Adverse events were not clearly different between pravastatin and either pitavastatin or atorvastatin, but harms were often not reported, or occurred infrequently. Rhabdomyolysis was not reported in any trial.

APPENDIX A. QUALITY ASSESSMENTS OF INCLUDED TRIALS

Author, Year Study Name	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?	Patient blinded?	Intention to treat?	Acceptable level of overall attrition (≤20%)?	Acceptable level of differential attrition (<10%)?	Overall quality
Abe, 2015	Unclear	Unclear	Yes	Unclear	No	No	Yes	Yes	Yes	Fair
Ishigaki, 2014	Yes	Unclear	Yes; except fasting plasma glucose	Unclear	No	No	No; only for harms	Yes	Yes	Fair
Kurogi, 2013	Unclear	Unclear	Yes	No	No	No	No	No; 45% attrition	Unclear	Poor
Lee, 2014 SAPHIRE	Unclear	Unclear	Yes	Unclear	No	No	Yes	Yes	Yes	Fair
Liu, 2013 PAPAGO-T	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Matsushita, 2016	Unclear	Unclear	Unclear (NR for all randomized, and differences as reported)	Unclear for clinical and cholesterol outcomes	Unclear	Unclear	No: 14% excluded after randomization	Yes	Yes	Fair for cholesterol Poor for harms
Sponseller, 2014	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Tani, 2015	Unclear	No (sealed envelope)	Unclear (13% difference in % male)	Unclear	No	No	Yes (3.7% excluded, though N's NR in Results)	Unclear	Unclear	Fair
Watanabe, 2015	Unclear	Unclear	Unclear; NR for 4 excluded patients	Unclear for cholesterol; yes for some imaging	Unclear	Unclear	No; excluded 4 patients (17%), 3 for worsening comorbidities	Yes	Unclear	Poor
Yoshida, 2013 VISION	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Fair (possibly poor)

Shading indicates trials identified in the present scan