



# Evidence-based Practice Center Systematic Review Protocol

## Project Title: Update of Comparative Effectiveness of Lipid-Modifying Agents

### I. Background and Objectives for the Systematic Review

#### Epidemiology and Practice Guidelines

Cardiovascular disease (CVD) affects 83.6 million Americans.<sup>1</sup> CVD includes a variety of conditions such as myocardial infarction, stroke, heart failure, arrhythmia, heart valve disease, and hypertension. In 2009, CVD contributed to 32.3 percent of U.S. deaths and is a leading cause of disability.<sup>1</sup> Atherosclerosis plays a major role in the development of certain cardiovascular diseases—coronary heart disease (CHD) including myocardial infarction, angina, and heart failure and cerebrovascular accident. These atherosclerotic diseases affect 15.4 million Americans.<sup>1</sup>

Elevated blood lipids are a major risk factor for atherosclerotic CVD. Abnormal lipoprotein metabolism predisposes individuals to atherosclerosis, especially increased concentrations of apolipoprotein B (apo B)-100-containing low-density lipoprotein (LDL-c). Oxidized LDL is atherogenic, causing endothelial damage, alteration of vascular tone, and recruitment of monocytes and macrophages. Many studies have underscored the importance of LDL-c in development of atherosclerotic CVD.<sup>2,3</sup> Due to the consistent and robust association of higher LDL-c levels with atherosclerotic CVD across experimental and epidemiologic studies, therapeutic strategies to decrease risk have focused on LDL-c reduction as the primary goal. The trial results are most compelling regarding the reduction of CHD by lowering LDL-c.<sup>4,5</sup> Based on this evidence, the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) report established three CHD risk strata together with guidelines regarding the initiation of treatment and therapeutic targets based on LDL-c cutoffs. The NCEP-ATP III defined the highest risk individuals as those with established CHD, other clinical atherosclerotic CVD such as cerebrovascular accident, or multiple risk factors for atherosclerotic CVD. These high-risk individuals have a 10-year CHD risk greater than 20 percent, and their LDL-c target is less than 100 mg/dL. Moderate-risk patients are those with two or more risk factors and a 10-year CHD risk less than 20 percent. The LDL target for moderate-risk patients is less than 130 mg/dL, but the threshold for starting drug therapy in these patients depends on their CHD risk level. For moderate-risk patients with a 10-year CHD risk of 10 to 20 percent, providers should consider drug therapy if the LDL-c is above 130 mg/dL; whereas for moderate-risk patients with a 10-year CHD risk less than 10 percent, drug therapy does not need to be considered until the LDL-c reaches 160 mg/dL.

Following release of the NCEP-ATP III guidelines in 2002, five major trials were published that led to a revision of these guidelines in 2004.<sup>6</sup> These revised guidelines expanded the



population for whom lipid-lowering therapy was recommended.<sup>7</sup> Diabetes was now considered a CHD risk equivalent, which placed patients with diabetes in the high-risk category. In addition, more aggressive targets were advocated as a therapeutic option for individuals at the highest risk. These “very high-risk patients” were defined as those with acute coronary syndromes, multiple major risk factors (especially diabetes and smoking), severe and poorly controlled risk factors, and multiple risk factors for metabolic syndrome. The previous target of LDL-c below 100 mg/dL was supplemented with an optional goal of LDL-c below 70 mg/dL in these very high-risk patients who already have baseline LDL-c below 100 mg/dL. While this new, lower target of LDL-c was supported by two trials,<sup>8,9</sup> additional trials are needed to confirm this finding and make this target a definitive recommendation.

## Current Practices and Decisional Uncertainty

The NCEP-ATP III provided guidelines both for when to initiate lipid-lowering therapy and also for LDL-c targets for optimal CHD-risk reduction. Lipid lowering in high-risk populations is likely to require treatment modification (intensifying therapy through dose increases or additional agents) to achieve LDL-c targets and achieve maximal benefit.

Current medication options for lipid-lowering therapy include 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, bile acid sequestrants, a cholesterol-absorption inhibitor, fibrates, nicotinic acid, and omega-3 fatty acids, which all have various mechanisms of action and pharmacokinetic properties. The most widely prescribed lipid-lowering agents are the HMG-CoA reductase inhibitors or “statins.” These agents reduce the production of cholesterol in the liver by binding with the enzyme responsible for its production. In addition to their lipid effects, statins may also have other cardiovascular effects, such as contributing to regression of atherosclerosis<sup>10</sup> and plaque stabilization,<sup>11</sup> decreasing inflammation,<sup>12</sup> and improving endothelial dysfunction.<sup>13</sup> Bile acid sequestrants (BAS) bind bile acids in the bowel, thereby preventing reabsorption of bile from the intestine. As a result, there is less intrahepatic cholesterol, causing synthesis of LDL receptors that bind plasma LDL. Bile acids have minimal effect on high-density lipoprotein (HDL). The cholesterol absorption inhibitor, ezetimibe, acts on the sterol transporter NPC1L1. Fibrates do not influence lipid synthesis but rather reduce the levels of fatty acids in the blood. They lower triglycerides, increase HDL, and decrease LDL. Niacin (nicotinic acid) inhibits synthesis of very low-density lipoprotein (VLDL) and LDL. The mechanism of omega-3 fatty acids is not fully understood, but they may inhibit acyl-CoA:1,2 diacylglycerol acyltransferase, increase hepatic beta-oxidation, reduce the hepatic synthesis of triglycerides, or increase plasma lipoprotein lipase activity.

Multiple trials have evaluated the effects of cholesterol reduction on cardiovascular events and mortality. In patients without clinical evidence of CHD, statins have decreased nonfatal myocardial infarctions and CHD mortality,<sup>14</sup> the incidence of a first major coronary event,<sup>15,16</sup> and all-cause mortality.<sup>17</sup> In patients with known CHD or coronary equivalents such as diabetes, statins reduce major coronary events, cardiovascular mortality, and all-cause mortality.<sup>18,19</sup> There is ongoing debate about whether multiple agents should be used if LDL-c goals are not achieved with statins alone. There are potential benefits to treating with multiple agents due to the unique mechanisms of action of the other lipid-lowering agents. For example, a fibrate or niacin in combination with a statin may increase HDL and decrease triglycerides above what is achieved with statin treatment alone.<sup>20</sup> There may also be fewer statin-related side effects, such as myalgias and liver enzyme elevations, with lower statin doses. Despite these theoretical benefits



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and generally favorable effects of combination regimens on surrogate markers in clinical trials, combination regimens have not consistently been shown to improve clinical outcomes.<sup>20-23</sup> In addition, the use of multiple agents in combination therapy may increase the risk of serious adverse events when compared with statin monotherapy.

To provide additional guidance to clinicians treating patients with moderate or high CHD risk, this comparative effectiveness review (CER) will address long-term benefits and rates of serious adverse events (SAEs) associated with coadministration of different lipid-modifying agents compared with higher dose statin monotherapy. The CER will examine surrogate markers of CHD events including lipid levels and atherosclerosis, as well as side effects/tolerability and adherence to combination therapy versus statin monotherapy. Differences in clinical/surrogate benefits and harms will be evaluated in the following subgroups: patients with diabetes, patients with established vascular disease, females, patients older than 80, participants of African and Asian descent, and Hispanics.

This CER is an update of a 2009 CER produced for the Agency for Health Research and Quality (AHRQ) Effective Healthcare Program. The previous CER initially intended to examine the long-term benefits and rates of serious adverse effects of coadministration of different lipid-lowering agents versus higher dose statin monotherapy for patients at high CHD risk (10-year risk > 20%).<sup>24,25</sup> However, the authors found a paucity of evidence to address this question, so they conducted additional analyses unrestricted by patient risk, statin type, and statin dose. Despite this increase in scope, the authors concluded that there was insufficient evidence to determine whether combination therapy held benefit over monotherapy. Since the initial CER, several large randomized controlled trials<sup>20,23</sup> and smaller randomized trials<sup>26-31</sup> including efficacy and safety outcomes have been published. The evidence base for all three Key Questions (KQs) has been expanded, necessitating an update of the previous CER. For the current CER, we will cover patients at moderate and high CHD risk, which we define as a 10-year CHD risk greater than 10 percent or an LDL greater than 160 mg/dL. Limiting the scope of this review to only high-risk patients would limit its clinical relevance, as moderate-risk patients may require therapy intensification to reach their LDL goals. However, we will exclude lower risk patients with a 10-year CHD risk less than 10 percent, as they are likely to achieve their LDL goal with typical statin monotherapy.

### **Potential Impact of a Comparative Effectiveness Review**

A large number of Americans fall into populations recommended for lipid-modifying therapy, and many require intense treatment to reach their LDL-c targets. For this CER, populations requiring intensive lipid lowering are considered to be those with a 10-year risk of CHD greater than 20 percent or a baseline LDL-c of at least 190 mg/dL (high-risk patients). We will also examine moderate-risk patients, that is, those with a 10-year risk of CHD of 10 to 20 percent or an LDL-c of at least 160 mg/dL. Lipid lowering in these populations is likely to require treatment modifications in order to achieve LDL-c targets and maximal clinical benefit. This systematic review is intended to help patients and providers understand the evidence supporting the different options for treatment modification.

### **Expected Use of the Proposed Report**

The results of the proposed report will be of use to healthcare providers, healthcare policymakers, and guideline developers seeking to optimize the status of patients to decrease their CHD risk. The results will help provide an evidence base for future practice guidelines to influence patient management.

## II. The Key Questions

<b>KQ 1:</b>	For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits and rates of serious adverse events of coadministration of different lipid-modifying agents (i.e., a statin plus another lipid-modifying agent) when compared with higher dose statin monotherapy?
<b>KQ 2:</b>	Do these regimens differ in reaching LDL targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?
<b>KQ 3:</b>	When compared with higher dose statins and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

### PICOTS Criteria

The PICOTS (**p**atients, **i**nterventions, **c**omparators, **o**utcomes, **t**iming, and **s**etting) for the CER are as follows:

- **Population(s)**

Adults with high CVD risk (10-year CHD risk  $\geq 20\%$  and/or a mean LDL  $\geq 190$  mg/dL) and moderate CVD risk (10-year CHD risk 10–20% and/or a mean LDL  $\geq 160$  mg/dL)

- **Intervention**

- **Statin in a lower dose + another lipid-lowering medication including:**

- Bile acid sequestrants – cholestyramine and colestipol
- Ezetimibe
- Fibric acids – fenofibrate, fenofibric acid, and gemfibrozil
- Nicotinic acid – niacin
- Omega-3-acid ethyl esters
- Prepackaged combinations of lipid-lowering medications – for example, atorvastatin + ezetimibe, lovastatin + niacin, simvastatin + ezetimibe, and simvastatin + niacin

- **Comparator**

- **Higher dose statin monotherapy:**

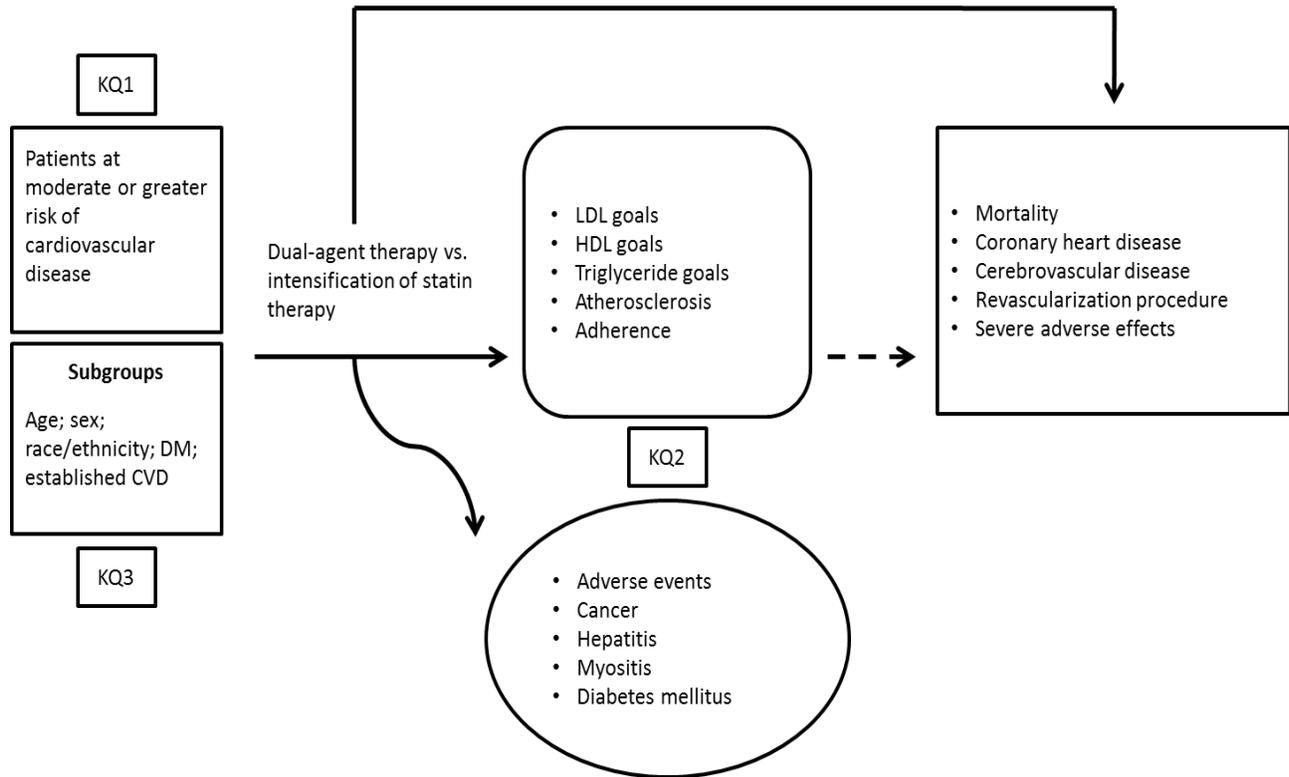
- Atorvastatin
- Fluvastatin and fluvastatin XL
- Lovastatin
- Pitavastatin



- Pravastatin
  - Rosuvastatin
  - Simvastatin
- **Outcomes**
    - **Clinical outcomes:**
      - All-cause mortality and vascular death
      - Fatal myocardial infarction (MI), nonfatal MI, any or unspecified MI, and acute coronary syndrome (ACS; unstable angina or acute MI)
      - Hemorrhagic stroke, ischemic stroke, any or unspecified stroke, and transient ischemic attack (TIA)
      - Carotid endarterectomy, percutaneous coronary intervention, coronary artery bypass graft, and any or unspecified revascularization procedure
    - **Surrogate clinical outcomes:**
      - Attainment of the NCEP-ATP III LDL-c target, LDL-c, HDL-c, and the total cholesterol (TC):HDL-c ratio
      - Non-HDL-c and triglycerides in a subgroup with diabetes mellitus
      - Measures of carotid or coronary atherosclerosis: arterial intima-media thickness, plaque area, plaque volume, arterial calcification, and/or measure of stenosis
    - **Adherence and harms:**
      - Treatment adherence as defined by the study investigator
      - SAEs as defined by the study investigator (e.g., an event that results in death, hospitalization, disability, or a birth defect)
      - Participants experiencing at least one adverse event; withdrawal due to an adverse event; cancer; serum aspartate transaminase and/or alanine aminotransferase elevated  $\geq 3$  times the upper limit of normal and/or hepatitis; myalgia; creatine phosphokinase elevated  $\geq 10$  times the upper limit of normal; rhabdomyolysis (investigator defined); newly diagnosed diabetes mellitus (investigator defined); a hemoglobin A<sub>1c</sub>  $\geq 6.5$  percent; a fasting glucose  $\geq 126$  mg/dL; and newly diagnosed acute kidney injury and chronic kidney disease (investigator defined)
  - **Timing and Study Design**
    - Randomized controlled trial (RCT) of any duration
    - Nonrandomized study (NRS) if it is a continuation of an RCT, is over 24 weeks in duration, and investigates clinical outcomes, SAEs, or cancer
    - U.S. Food and Drug Administration (FDA) reports for SAEs and harms of any duration
  - **Settings**
    - Outpatient setting

### III. Analytic Framework

Figure 1. Analytic Framework for Comparative Effectiveness of Lipid-Modifying Agents



Abbreviations: CVD = cardiovascular disease; DM = diabetes mellitus; HDL = high-density lipoprotein; KQ = key question; LDL = low-density lipoprotein

### IV. Methods

We will conduct a systematic review of the comparative effectiveness of lipid-modifying agents in adults at moderate or high risk for cardiovascular disease.

#### A. Criteria for Inclusion/Exclusion of Studies in the Review

Inclusion and exclusion criteria are provided in Table A.

**Table A. List of inclusion/exclusion criteria**

PICOTS	Inclusion	Exclusion
<b>Population</b>	<ul style="list-style-type: none"> <li>Adults with moderate (10-year CHD risk of 10–20% or an LDL <math>\geq</math>160 mg/dL) or high (10-year CHD risk <math>\geq</math>20% or an LDL <math>\geq</math>190 mg/dL) CVD risk</li> </ul>	<ul style="list-style-type: none"> <li>Adults with low CVD risk (CHD risk &lt;10% or LDL &lt; 160 mg/dL)</li> <li>Adults with homozygous FH</li> <li>Animal studies</li> <li>In vitro studies</li> </ul>

<p><b>Interventions</b></p>	<p><b>Statin (in a lower dose) + other lipid-lowering medications including:</b></p> <ul style="list-style-type: none"> <li>• Bile acid sequestrants – cholestyramine, colestipol, and colesevelam</li> <li>• Ezetimibe</li> <li>• Fibric acids – fenofibrate, fenofibric acid, and gemfibrozil</li> <li>• Nicotinic acid – niacin (IR, SR, or ER)</li> <li>• Omega-3-acid ethyl esters</li> <li>• Prepackaged combination lipid-lowering medications – atorvastatin + ezetimibe, lovastatin + niacin, simvastatin + ezetimibe, and simvastatin + niacin</li> </ul>	<ul style="list-style-type: none"> <li>• Lifestyle modifications only – diet, consumption of plant stanol/sterols, exercise, and fiber supplementation</li> <li>• Drugs approved only for treatment of homozygous FH – mipomersen and lomitapide</li> <li>• Drugs not approved by the FDA – cerivastatin, mevastatin, colestimide, clofibrate, cirprofibrate, bezafibrate, niacin/laropiprant, cholesterylester transfer protein inhibitors, and PCSK9 inhibitors</li> <li>• Prepackaged combination medications that include non-lipid-lowering agents – statin + calcium channel blocker, statin + DPP-4 inhibitor, and statin + TZD</li> <li>• Any eligible drug in nontherapeutic or unapproved doses</li> <li>• Any nonapproved investigational agent of one of the included drug classes</li> </ul>
<p><b>Comparisons of Interest</b></p>	<p><b>Higher dose statin monotherapy:</b></p> <ul style="list-style-type: none"> <li>• Atorvastatin, fluvastatin, fluvastatin XL, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin</li> </ul>	<p>If there is no comparison, the study will be excluded.</p>
<p><b>Outcomes</b></p>	<p><b>Clinical outcomes</b></p> <ul style="list-style-type: none"> <li>• All-cause mortality</li> <li>• Vascular death</li> <li>• Fatal MI, nonfatal MI, any or unspecified MI, and ACS (unstable angina or acute MI)</li> <li>• Hemorrhagic stroke, ischemic stroke, any or unspecified stroke, TIA</li> <li>• CEA, PCI, CABG, and any or unspecified revascularization procedure</li> </ul> <p><b>Surrogate clinical outcomes</b></p> <ul style="list-style-type: none"> <li>• Attainment of the NCEP-ATP III LDL-c target, LDL-c, HDL-c, and TC:HDL-c ratio</li> <li>• Non-HDL-c and triglycerides in a diabetic subgroup</li> <li>• Measures of carotid or coronary atherosclerosis (arterial intima-media thickness, plaque area, plaque volume, arterial calcification, and/or measure of</li> </ul>	<p>Composite outcomes (e.g., major adverse cardiac event)</p>



	stenosis)  <b>Adherence and harms</b>	
	<ul style="list-style-type: none"> <li>• Treatment adherence (investigator defined)</li> <li>• SAE (explicitly stated)</li> <li>• Participants experiencing at least one adverse event; withdrawal due to an adverse event; cancer; serum AST and/or serum ALT elevated <math>\geq 3</math> times the ULN and/or hepatitis; myalgia; CPK elevated <math>\geq 10</math> times the ULN; rhabdomyolysis (investigator defined); newly diagnosed diabetes mellitus (investigator defined); hemoglobin A1c <math>\geq 6.5\%</math>; fasting glucose <math>\geq 126</math> mg/dL; a new diagnoses of AKI; and CKD (investigator-defined)</li> </ul>	
<b>Type of Study and Timing</b>	<ul style="list-style-type: none"> <li>• RCT of any duration</li> <li>• NRS if it is a continuation or extension of an RCT over 24 weeks in duration and investigates clinical outcomes, SAEs, and/or harms</li> <li>• FDA reports on SAEs and/or harms</li> </ul>	<ul style="list-style-type: none"> <li>• Other observational designs</li> <li>• Qualitative studies</li> <li>• Publications with no original data (e.g., editorials, letters, comments, reviews)</li> <li>• Published only as abstracts</li> <li>• Indirect comparisons</li> <li>• Crossover trials with fewer than 4 weeks washout</li> <li>• Crossover trials without paired observations, within-person differences, or precrossover data.</li> </ul>
<b>Publication</b>	<ul style="list-style-type: none"> <li>• Studies published after 05/01/2008</li> <li>• Studies included in the previous CER that meet our current eligibility criteria</li> </ul>	<ul style="list-style-type: none"> <li>• Non-English-language publication</li> <li>• Full text not presented or unavailable</li> <li>• Studies included in the previous CER that do not meet our current eligibility criteria</li> </ul>

Abbreviations: ACS = acute coronary syndrome; AKI = acute kidney injury; ALT = alanine aminotransferase; AST = aspartate transaminase; CABG = coronary artery bypass graft; CEA = carotid endarterectomy; CER = comparative effectiveness review; CHD = coronary heart disease; CKD = chronic kidney disease; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase IV; ER = extended release; FDA = U.S. Food and Drug Administration; HDL = high-density lipoprotein; IR = immediate release; LDL = low-density lipoprotein; MI = myocardial infarction; NCEP-ATP III = National Cholesterol Education Program Adult Treatment Panel III; NRS = nonrandomized study; PCI = percutaneous coronary intervention; PCSK9 = proprotein convertase subtilisin/kexin type 9; RCT = randomized controlled trial; SAE = serious adverse event; SR = sustained release; TC = total cholesterol; TIA = transient ischemic attack; TZD = thiazolidinedione; ULN = upper limit of normal

**Table B. List of FDA-approved lipid lowering medications or pharmaceutical agents**

Generic Name	U.S. Trade Name	Route	Class
Atorvastatin	Lipitor <sup>®</sup>	Oral	HMG-CoA reductase inhibitor (statin)
Fluvastatin	Lescol <sup>®</sup>	Oral	HMG-CoA reductase inhibitor (statin)
Fluvastatin XL	Lescol XL <sup>®</sup>	Oral	HMG-CoA reductase inhibitor (statin)
Lovastatin	Mevacor <sup>®</sup>	Oral	HMG-CoA reductase inhibitor (statin)
Pitavastatin	Livalo <sup>®</sup>	Oral	HMG-CoA reductase inhibitor (statin)
Pravastatin	Pravachol <sup>®</sup>	Oral	HMG-CoA reductase inhibitor (statin)
Rosuvastatin	Crestor <sup>®</sup>	Oral	HMG-CoA reductase inhibitor (statin)
Simvastatin	Zocor <sup>®</sup>	Oral	HMG-CoA reductase inhibitor (statin)
Cholestyramine	Prevalite <sup>®</sup>	Oral	Bile acid sequestrant
Colesevelam	Welchol <sup>®</sup>	Oral	Bile acid sequestrant
Colestipol	Colestid <sup>®</sup> ; Flavored Colestid <sup>®</sup>	Oral	Bile acid sequestrant
Ezetimibe	Zetia <sup>®</sup>	Oral	Cholesterol absorption inhibitor
Fenofibrate	Tricor <sup>®</sup> ; Triglide <sup>®</sup> ; Lipofen <sup>®</sup> ; Fenoglide <sup>®</sup>	Oral	Fibric acid
Fenofibric acid	Fibricor <sup>®</sup> ; Trilipix <sup>®</sup>	Oral	Fibric acid
Gemfibrozil	Lopid <sup>®</sup>	Oral	Fibric acid
Niacin	Niaspan <sup>®</sup> ; Niacor <sup>®</sup>	Oral	Nicotinic acid
Omega-3-acid ethyl ester	Lovaza <sup>®</sup> ; Omacor <sup>®</sup>	Oral	Omega-3-acid ethyl ester
Icosapent ethyl	Vascepa <sup>®</sup>	Oral	Omega-3-acid ethyl ester
Atorvastatin + ezetimibe	N/A – Under FDA review	Oral	HMG-CoA reductase inhibitor (statin) + ezetimibe
Lovastatin + niacin	Advicor <sup>®</sup>	Oral	HMG-CoA reductase inhibitor (statin) + nicotinic acid
Simvastatin + ezetimibe	Vytorin <sup>®</sup>	Oral	HMG-CoA reductase inhibitor (statin) + ezetimibe
Simvastatin + niacin	Simcor <sup>®</sup>	Oral	HMG-CoA reductase inhibitor (statin) + nicotinic acid

Abbreviations: FDA = U.S. Food and Drug Administration; HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; N/A = not applicable; XL = extended release

## B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

We will develop a search strategy for MEDLINE<sup>®</sup>, accessed via PubMed<sup>®</sup>, based on an analysis of the medical subject headings (MeSH<sup>®</sup>) terms for all potential relevant publications and text words of key articles identified a priori. The search will be updated during the peer review process. We will search the following databases for primary studies: MEDLINE, EMBASE<sup>®</sup>, and the Cochrane Central Register of Controlled Trials (CENTRAL). Our preliminary search strategy for MEDLINE is shown in Appendix A.

The initial literature search for this project included MEDLINE from 1966 to May 2009, EMBASE from 1980 to May 2009, and the Cochrane Library to the third quarter of 2008. We will include an overlap in search dates, per AHRQ guidance on updating reviews,<sup>32</sup> searching MEDLINE from May 2008 to January 2013, EMBASE from May 2008 to January 2013, and the Cochrane library from the fourth quarter of 2007 to the first quarter of 2013.



We will also review the reference lists of each included article, relevant review articles, and related systematic reviews. We will include extensions of RCTs of over 24 weeks, as these will provide long-term followup of a trial population where certain adverse effects may be identified that were not identified within the original study period. We will also assess for serious and rare harms by including and reviewing harms reports from the FDA, as well as the scientific information packets provided by pharmaceutical manufacturers of all drugs.

To identify ongoing clinical trials, we will search the World Health Organization International Trials Registry (<http://apps.who.int/trialsearch/>) and ClinicalTrials.gov (<http://clinicaltrials.gov>) and will use the information provided in the Scientific Information Package provided by the AHRQ Scientific Resource Center on the drugs included in this study.

## C. Data Abstraction and Data Management

We will use DistillerSR (Evidence Partners, Ottawa, Canada) to manage the screening process. DistillerSR is a Web-based database management program that manages all levels of the review process. All applicable citations identified by the search strategies are uploaded to the system and reviewed in the following manner:

1. **Abstract screening.** Two investigators will independently review abstracts, which will be excluded if both investigators agree that the article meets one or more of the exclusion criteria listed in Table A. Differences between investigators regarding abstract eligibility will be tracked and resolved through consensus adjudication. Relevant reviews, including systematic reviews and meta-analyses, will be tagged for a search of their reference lists.
2. **Full-text screening.** Citations promoted on the basis of the abstract review will undergo another independent parallel review using the full text of the articles to determine if they should be included in the final qualitative and quantitative systematic review and meta-analysis. The differences regarding article inclusion will again be tracked and resolved through consensus adjudication. We will also screen at the full-text level all studies included in the previous CER to ensure that they meet the current eligibility criteria.

We will use a systematic approach to extract the data to minimize the risk of bias in this process. We will create standardized forms for data extraction, which will be pilot tested. By creating standardized forms for data extraction, we will maximize consistency in identifying pertinent data available for synthesis. Each article will undergo double review by study investigators for data abstraction. The second reviewer will confirm the first reviewer's data abstraction for completeness and accuracy. A third reviewer will audit a random sample of articles assessed by the first two reviewers to ensure consistency in the data abstraction of the articles. Articles referring to the same study will be abstracted on a single review form if reporting the same data or on separate forms if necessary with clear information provided that the results should be interpreted as from the same study. Reviewers will not be masked to the articles' authors, institution, or journal. For all articles, reviewers will extract

information on general study characteristics (e.g., study design, study period, and followup), study participants (e.g., age, sex, race/ethnicity, etc.), eligibility criteria, interventions (e.g., medication name, medication dose), outcome measures and the method of ascertainment, and the results of each outcome, including measures of variability. We will integrate the data previously abstracted from the previous CER for all studies from this previous review that will be included in this current review. If these previous data are missing any elements included in our current abstraction forms, then we will abstract this information from these articles.

We will complete the article data abstraction process using the Systematic Review Data Repository™ (SRDR), a Web-based repository. This resource serves as both an archive and a data extraction tool. Data will be exported from the SRDR into a project-specific Access database (Microsoft, Redmond, WA) to serve as archived or backup copies and to create detailed evidence tables and summary tables.

We have obtained data files from the previous CER. We will examine the contents of these data files to determine if additional data need to be abstracted from these articles (e.g., population characteristics).

## D. Assessment of Methodological Risk of Bias of Individual Studies

The assessment of risk of bias of included trials will be conducted independently and in duplicate based on the Cochrane Collaboration’s Risk of Bias Tool.<sup>33</sup> For nonrandomized studies (NRS), we will use the Newcastle Ottawa Scale.<sup>34</sup> We will supplement these tools with additional assessment questions, such as use of appropriate analysis, based on recommendations in the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter *Methods Guide*).<sup>35</sup>

## E. Data Synthesis

Qualitative synthesis will be completed, grouped by type of intervention (i.e., statin + ezetimibe vs. statin monotherapy; statin + nicotinic acid vs. statin monotherapy). We will integrate the results of all trials (RCTs + NRSs) qualitatively. Our comparison of a lower dose statin in combination therapy with higher dose statin monotherapy will be statin specific. In order to avoid multiple comparisons across numerous permutations of lower versus higher dose statins, we will group statins based on their potency to reduce LDL-c, as determined by a recent systematic review.<sup>36</sup> This represents a change from the approach used in the original CER, which grouped statins according to dose; but, we believe that this new categorization more accurately equilibrates the different statins.

**Table C. List of different doses of specific statins based on potency to reduce LDL-c**

Statin	Atorvastatin (mg/day)	Fluvastatin (mg/day)	Fluvasatin XL (mg/day)	Lovastatin (mg/day)	Pitavastatin (mg/day)	Pravastatin (mg/day)	Rosuvastatin (mg/day)	Simvastatin (mg/day)
Low potency (<30% LDL reduction)	5	20 and/or 40	--	5 and/or 10 and/or 20	1	10 and/or 20 and/or 40	--	10
Mid potency (30-40%)	10	80	80	40 and/or 80	2 and/or 4	80	5 and/or 10	20



LDL reduction)								
High potency (>40% LDL reduction)	20 and/or 40 and/or 80	--	--	--	--	--	20 and/or 40	40 and/or 80*

\*Studies that use 80-mg simvastatin in statin-naïve patients will be excluded.

Abbreviations: LDL = low-density lipoprotein; LDL-c = apolipoprotein B-100--containing low-density lipoprotein; XL = extended release

We will create a set of detailed evidence tables containing all information abstracted from eligible studies. We will include data from the initial report, which will be integrated with the new data we abstract during the current CER. We will conduct meta-analyses of summary data when there are sufficient data (at least three studies of the same design) and studies are sufficiently homogenous with respect to key variables (population characteristics, intervention, and outcome). RCTs and NRSs will be analyzed separately. All analyses will be intention to treat. Statistical significance (will be set at a two-sided alpha of 0.05). Studies that are not amenable to pooling will be summarized qualitatively.

For studies amenable to pooling with meta-analyses, we will calculate a weighted mean difference using a random effects model with the DerSimonian and Laird formula for continuous outcomes.<sup>37</sup> We will calculate a pooled effect estimate of the relative risk between trial arms from RCTs for dichotomous outcomes, with each study weighted by the inverse variance, using a random effects model with the DerSimonian and Laird formula for calculating between-study variance.<sup>37</sup> We will evaluate for statistical heterogeneity among studies using an I<sup>2</sup> statistic and anticipate statistical heterogeneity. A value greater than 50 percent will be considered to have substantial statistical heterogeneity. If we find substantial heterogeneity, we will attempt to determine potential reasons by conducting a meta-regression if covariate information (age, sex, and dose) is available.

For sparse-data meta-analysis, we will employ the Peto odds ratio method when event rates are less than 1 percent.<sup>38</sup> When between-event rates are between 5 to 10 percent, substantial differences between the N of two arms, or when the effect size is large, dichotomous data will be meta-analyzed using the Mantel-Haenszel method without continuity correction.<sup>39</sup> Dichotomous data with zero values in both arms will not be included in the meta-analyses.

Publication bias may be examined using Begg’s and Eggers tests (with an alpha of 0.10) including evaluation of the asymmetry of funnel plots for each comparison of interest for the outcomes where meta-analyses are conducted.<sup>40</sup> Criteria for testing for funnel plot asymmetry will be at least 10 studies of unequal sizes contributing quantitative data for which there are no apparent relationship between study size and between study clinical or methodological diversity.<sup>41</sup> All meta-analyses will be conducted using STATA<sup>®</sup> (StataCorp, College Station, TX).

We will report benefits and harms for subgroups of interest including age groups, race, ethnicity, and gender. We will examine these subgroups by evaluating effect in both moderate and high CHD risk, as well as stratified by CHD risk. We will also examine subgroups of patients of higher CHD risk including patients with diabetes mellitus, patients with pre-existing CVD including those with established vascular or cerebrovascular diseases, and patients with an LDL-c of 190 mg/dL or above.

## F. Grading the Strength of Evidence for Individual Comparisons and Outcomes

At the completion of our review, two reviewers will independently grade the strength of evidence on key outcomes—including, all-cause mortality, vascular death, SAEs, and attainment of NCEP-ATP III LDL-c goals—by adapting a grading scheme recommended in the *AHRQ Methods Guide*.<sup>42</sup> We will consider four domains: risk of bias of included studies, directness, consistency, and precision. We will grade evidence for each outcome identified in the KQs.

We will classify evidence pertaining to KQs 1, 2, and 3 into four categories: (1) “high” grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); (2) “moderate” grade (indicating moderate confidence that the evidence reflects the true effect, and further research may change our confidence in the estimate of the effect and may change the estimate); (3) “low” grade (indicating low confidence that the evidence reflects the true effect, and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) “insufficient” grade (evidence is unavailable). The grade of evidence for each KQ will be based on consensus.

The strength of evidence in the initial CER had been evaluated before AHRQ guidance was developed for the Evidence-based Practice Center Program. We have received data files from the original CER from the University of Ottawa and will re-evaluate the prior trials and redo the grading.

## G. Assessing Applicability

We will consider elements of the PICOTS framework when evaluating the applicability of evidence to answer our KQs as recommended in the *Methods Guide*.<sup>35</sup> We will consider important population characteristics (e.g., women, minorities, diabetics), treatment characteristics (e.g., statin type, statin potency), and settings (e.g., a study conducted in a non-U.S. health care setting) that may cause heterogeneity of treatment effects and limit applicability of the findings.

### Summary of Changes From the Previous Systematic Review

- **Population**

We will include adults at moderate and high risk of CVD (the previous report had no restrictions by patient CVD-risk level). We will specifically exclude studies of patients with homozygous familial hypercholesterolemia.

- **Intervention**

We will include drugs that were not previously FDA-approved at the time of the previous review. Drugs that will potentially be approved by the FDA in the near future will be included, specifically the prepackaged combination of atorvastatin + ezetimibe.



- **Outcomes**

We will include diabetes mellitus and acute kidney injury/chronic kidney disease as potential harms.

- **Type of Study and Timing**

The only observational studies we will include will be extensions of RCTs looking at long-term outcomes. The previous CER considered any NRS over 24 weeks in duration.

- **Data Synthesis**

We will group statins according to their potency to reduce LDL-c.

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## **VI. Definition of Terms**

Not applicable.

## **VII. Summary of Protocol Amendments**

Not applicable.

## **VIII. Review of Key Questions**

For all EPC reviews, Key Questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, the Key Questions were posted for public comment and finalized by the EPC after review of the comments.

## **IX. Key Informants**

Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## **X. Technical Experts**

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## **XI. Peer Reviewers**

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical Briefs, be published 3 months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

## **XII. EPC Team Disclosures**

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

### **XIII. Role of the Funder**

This project was funded under Contract No. HHS 2902012000071 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

## Appendix A. Search Strategy

### PubMed

“Hydroxymethylglutaryl-CoA Reductase Inhibitors” [mh] OR “Heptanoic Acids” [mh] OR “Heptanoic Acids” [tiab] OR statin\*[tiab] OR “reductase inhibitor\*”[tiab] OR Simvastatin [mh] OR Simvastatin [tiab] OR Atorvastatin [nm] OR Atorvastatin [tiab] OR Rosuvastatin [nm] OR Rosuvastatin [tiab] OR Pravastatin [mh] OR Pravastatin [tiab] OR Lovastatin [mh] OR Lovastatin [tiab] OR Fluvastatin [nm] OR Fluvastatin [tiab] OR Pitavastatin[nm] OR Pitavastatin[tiab]

AND

(fatty acids, omega-3 [mh] OR “omega 3” [tiab] OR “fatty acids” [tiab] OR fatty acids, essential [MH] OR Dietary Fats, Unsaturated [MH] OR linolenic acids [MH] OR linolenic acids [tiab] OR fish oils [MH] OR “fish oils” [tiab] OR alpha linolenic acid[mh] OR “alpha linolenic acid” [tiab] OR linolenate[mh] OR linolenate[tiab] OR nervonic acid[nm] OR “nervonic acid”[tiab] OR timnodonic acid[mh] OR timnodonic acid[tiab] OR Mediterranean diet[MH] OR (Mediterranean[tiab] AND diet[tiab]) OR Flax[MH] OR flaxseed [MH] OR linseed [MH] OR rapeseed [MH] OR canola [MH] OR soybean [MH] OR walnut [MH] OR ((Flax[tiab] OR flaxseed [tiab] OR linseed [tiab] OR rapeseed [tiab] OR canola [tiab] OR soybean [tiab] OR walnut [tiab]) AND Oil[tiab]) OR cod liver oil[MH] OR “cod liver oil”[tiab] OR salmon[MH] OR salmon[tiab]OR mackerel[MH] mackerel[tiab] or tuna[MH] or tuna[tiab] or halibut[MH] or halibut[tiab] or seal[MH] or seal[tiab] or seaweed [MH] or seaweed [tiab] OR anticholesteremics [MH] OR anticholesteremics [tiab] OR bile acids[MH] OR “bile acids”[tiab] OR (bile[tiab] AND resin\*[tiab]) OR “bile acid sequestrant”[tiab] OR cholestyramine [MH] OR cholestyramine [tiab] OR colestyramin [MH] OR colestyramin [tiab] OR quantalan [MH] OR quantalan [tiab]OR questran [MH] OR questran [tiab] OR colesevelam[NM] OR colesevelam[tiab] OR Cholestyramine [MH] OR Cholestyramine [tiab] OR Colestipol [MH] OR Colestipol [tiab] OR colestilan[NM] OR colestilan[tiab] OR colestipol [MH] OR colestipol [tiab] OR ezetimibe[NM] OR ezetimibe[tiab] OR (cholesterol\*[tiab] AND inhibitors\*[tiab]) OR cholesterol inhibitors [MH] OR fibrates [MH] OR fibrates [tiab] OR fibric acid [nm] OR fibric acid [tiab] OR Clofibrac acid [MH] OR Clofibrac acid [tiab] OR Gemfibrozil [MH] OR Gemfibrozil [tiab] OR Procetofen [MH] OR Procetofen [tiab] OR fenofibrate [MH] OR fenofibrate [tiab] OR clofibrac acid [MH] OR clofibrac acid [tiab]OR procetofen[MH] OR procetofen[tiab] OR ciprofibrate[NM] OR ciprofibrate[tiab] OR niacin [MH] OR niacin [tiab] OR nicotinic acid[MH] OR nicotinic acid[tiab] OR niacin [MH] OR niacin [tiab] OR Zetia [NM] OR Zetia [tiab] OR Lopid [MH] OR Lopid [tiab] OR Tricor [MH] OR Tricor [tiab] OR Lofibra [MH] OR Welchol [NM] OR Welchol [tiab] OR Colestid [MH] OR Colestid [tiab] OR Questran [MH] OR Questran [tiab] OR Drug Therapy, Combination[MH] OR (combination[tiab] AND therapy[tiab]))

AND

(randomized controlled trial[pt] OR controlled clinical trial [pt] or randomized controlled trials[mh] or random allocation[mh] or double-blind method[mh] or single-blind method[mh] OR clinical trial[pt] or clinical trials[mh] or (“clinical trial”[tw]) OR ((singl\*[tw] OR doubl\*[tw] OR trebl\*[tw] OR tripl\*[tw]) AND (mask\*[tw] OR blind\* [tw])) OR (“latin square”[tw]) OR placebos[mh] OR placebo\*[tw] OR rando\*[tw] OR research design[mh:noexp]) Not (animal[mh] Not human[mh])

Filters: Publication date from 2008/01/01 to 2013/12/31