Published in final edited form as:
Prim Care. 2013 March ; 40(1): 195–211. doi:10.1016/j.pop.2012.11.003.

Hyperlipidemia as a Risk Factor for Cardiovascular Disease

Robert H. Nelson, MD[a,b,†]

[a]Assistant Professor of Medicine/Division of Endocrinology, Mayo College of Medicine, Rochester, MN 55905

[b]Assistant Professor of Family Medicine, Mayo College of Medicine, Rochester, MN 55905

Synopsis

Elevated levels of blood lipids are well documented risk factors for cardiovascular disease. Current classification schemes and treatment levels for hyperlipidemia are based on the National Cholesterol Education Panel's (NCEP) Adult Treatment Program-3 (ATP-III) guidelines. Statins are the preferred class of drugs to lower elevated low density lipoprotein cholesterol (LDL-C). There are other classes to augment or substitute for statins, such as ezetimibe, fibrates, niacin and dietary supplements. Extensive research over the last decade has raised the question whether or not ATP-III guidelines are sufficiently aggressive. New guidelines from ATP-IV are expected to be released in the near future, but in the meantime physicians are faced with uncertainty about how low to target LDL-C, whether to pharmacologically treat high density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels and how best to achieve target goals.

Keywords

Hypercholesterolemia; Hypertriglyceridemia; Dyslipidemia; Cardiometabolic Risk; CVD Risk Factors

Introduction

Modern primary care practitioners spend considerable time and effort on preventative medicine. Diagnosing and managing hyperlipidemia as a way to prevent cardiovascular disease (CVD) is a common activity for primary care physicians. According to Centers for Disease Control data from a survey of 1,492 physicians who provide ambulatory care in non-government settings, hyperlipidemia is second only to hypertension in the list of the 10 most common chronic conditions that were seen (1) The fact that hyperlipidemia is a strong risk factor for CVD is well established. Hyperlipidemia refers to elevated cholesterol, elevated TG or both. The problem can be due solely to hereditary factors, but more commonly it is an acquired condition. Physicians need to know the major categories of dyslipidemia and to have a well reasoned action plan for dealing with each one, including knowing when to refer a case to a lipidology specialist. It is the purpose of this paper to

[†]**to whom correspondence should be addressed at:** Endocrine Research Unit, Mayo Clinic, 200 First Street SW, Rochester, MN USA 55905, Telephone: 507-255-1480, Fax: 507-255-4828, nelson.robert1@mayo.edu.

Conflict of Interest:
Nil

review the categories of hyperlipidemia, the current treatment recommendations and the current controversies and unresolved questions. Some of the recent evidence based data (~2000 to current year) and studies regarding hyperlipidemia will be discussed.

Definitions of hyperlipidemia

For most primary care providers, hyperlipidemia is defined as elevations of fasting total cholesterol concentration which may or may not be associated with elevated TG concentration. However, lipids are not soluble in plasma, but are instead transported in particles known as lipoproteins. Therefore, classifications of hyperlipidemia are also based on abnormalities of lipoproteins. See Box 1.

The NCEP created a standard using lipid levels in 2001 that is still the most commonly used clinical classification (2). See Table 1. The NCEP is currently revising its recommendations with an updated version of ATP-III guidelines expected to be released in the autumn of 2012.

Significance of hyperlipidemia

Health care providers are concerned about hyperlipidemia because of the well established association between lipid concentrations and the risk of CVD, the leading cause of death in the United States (3). A landmark study that helped establish that therapeutic interventions to lower cholesterol levels result in reduced risk of cardiovascular morbidity or mortality was the Lipid Research Clinics Coronary Primary Prevention Trial, which was published in two parts (each using a different statistical analysis) in 1984 (4; 5). However, numerous other trials, both prior to and after 1984, also contributed to the evidence of a CVD-hyperlipidemia link. The scientific and medical communities took several decades to agree that this relationship truly exists. A complete history of the cholesterol controversy can be found in a multi-part review (available on line) which was published over a 3 year span in the Journal of Lipid Research (6–10).

Diagnosis

Most cases of hyperlipidemia are found because a lipid panel screen is done as a part of a routine health care evaluation or because plasma lipids are checked after a cardiovascular event. The United States Preventive Services Task Force has posted screening recommendations for lipid disorders on its web site (11). The group does not recommend universal screening. Its guidelines are summarized in Box 2.

Not all experts agree with these recommendations, primarily because they believe that the overall incidence of CVD in the United States is so high that screening should be more aggressive. For example, the American Heart Association states on its web site (12) that “The American Heart Association urges all Americans to have their physicians determine their total and HDL blood cholesterol levels. This is very important for those people with a family history of heart disease, high blood pressure or stroke.” Screening refers to testing lipids in people who are without symptoms or associated disease. Any person who is diagnosed with diseases related to hyperlipidemia (e.g. hypothyroidism, diabetes, renal insufficiency, etc.) should have a lipid evaluation as a part of the diagnostic workup. This also holds true for anyone who presents with evidence of CVD (e.g. angina, myocardial infarction, onset of claudication, discovery of a vessel bruit, etc.).

Classification of hyperlipidemia

Abnormal lipid profiles are generally a combination of abnormalities of the lipoprotein fractions noted in Box 1. The degree of increased risk of CVD depends on the exact pattern and the underlying cause. Primary care physicians do not necessarily need full knowledge of all hyperlipidemic syndromes, but all physicians should be fully aware of their own individual limitations and capabilities. It is vital to know common primary and secondary causes of elevated lipids and to recognize unusual patterns or physical findings that should trigger a referral to a lipidologist. Although rare in primary care practices, many genetic causes of hyperlipidemia carry an increased risk of premature CVD and/or other organ system disease. Some of these syndromes require different treatment than the usual primary care patient presenting with hyperlipidemia.

Hyperlipidemia can broadly be classified as isolated elevation of cholesterol, isolated elevated TG and elevations of both. The cause may be genetic, environmental or both. Table 2 is a list of genetic causes of hyperlipidemia with a brief clinical description including clues that should trigger consideration of a lipid specialty referral. In general, the clues to a genetic syndrome include very high cholesterol levels (> 300 mg/dL), very high TG levels (>500 mg/dL), xanthomas, strong family history of hyperlipidemia or early CVD, or lack of expected response to maximal therapeutic doses of lipid lowering agents.

Dyslipidemia has multiple secondary causes. These are listed in Table 3, which is divided into isolated cholesterol elevation, isolated TG elevation and a mixed pattern. An important secondary cause of high cholesterol is hypothyroidism. It is important to screen people with elevated cholesterol for hypothyroidism. This is due to the fact that hypothyroidism causes elevations of cholesterol and reduced thyroid hormone concentrations increase the risk of statin induced myopathy (13) Other important contributors to secondary hyperlipidemia include diabetes, renal disease and alcoholism. HIV is an important consideration both because the infection and the use of protease inhibitors can contribute to lipid abnormalities (14).

Evaluation and treatment of patient with hyperlipidemia

CVD risk analysis

An important step in the interpretation of lipid screening results is the performance of a cardiovascular risk assessment. This point is strongly emphasized in the report of ATP-III and in numerous peer reviewed journal articles reviewing the topic of lipid management. The basic principle is that the higher a person’s CVD risk, the greater the benefit in aggressively treating all modifiable risk factors, including hyperlipidemia. Any physician who is interpreting the results of a lipid panel needs to take the time to do a formal CVD risk analysis. One of the most commonly used validated instruments is the Framingham Risk Score. However, it has several limitations such as underestimating the risk in a high risk individual due to the absence of some important risk factors in the scoring system (15). Therefore, others have attempted to improve the scoring system in order to more precisely estimate the risk of a major cardiovascular event in differing groups (16; 17).

Novel risk factors

The emphasis on lowering LDL-C with statins has resulted in significant improvement in morbidity and mortality from CVD. However, despite the emphasis on control of LDL-C, a number of cardiac events occur in people without clinically abnormal LDL-C concentrations. This problem is often referred to as residual risk. One way of improving risk prediction and treatment has been to focus on non-HDL cholesterol levels rather than on just LDL-C. The reason for this is that other lipoprotein fractions contribute to the formation of

atherosclerosis. These particles are intermediate or end products of triglyceride rich lipoprotein (TGRL) catabolism, specifically very low density lipoprotein (VLDL) and chylomicrons. As triglycerides are removed from TGRLs by intravascular lipases, the particles become denser and have a greater portion of their composition as cholesterol. In the case of chylomicrons, which transport dietary fat, the end product of TG lipolysis is a small, dense Apo-B48 containing particle known as a chylomicron remnant. VLDL, which transports endogenously produced TG, has a more complex catabolism. In a simplified version, the catabolic steps can be thought of as a conversion of VLDL to intermediate density lipoproteins (IDL), which are then converted to LDL. The particles are defined by their different densities and TG:Cholesterol ratios, but all of them contain apoB-100. These remnant particles are believed to be significant contributors to CVD because the particles not eliminated by the liver (the preferred disposal site) are taken up in arterial walls to eventually become lipid laden macrophages, the well known foam cells that are a hallmark of early atherosclerosis. In a meta-analysis of 38,153 statin treated subjects in whom non-HDL-C, LDL-C and Apo-B were compared, all three markers were predictive of CVD, with non-HDL-C showing a slightly greater association than the other two (18). However, even though statistically non-HDL-C was the best predictor, the 95% confidence intervals of the hazard ratio of CVD for each of the 3 markers overlapped sufficiently that this study cannot be considered conclusive.

Additional, markers for risk factor analysis are based on the contribution to CVD.by inflammatory proteins and other cytokines. In 2011, a consensus panel of the National Lipid Association published a review of the clinical utility of various proposed markers. See Box 3 for a partial list of markers that have been proposed.

In general, alternative risk factor markers have had mixed results in clinical trials. Even the most positive studies have not shown a dramatic improvement in prediction of future CVD risk compared to traditional Framingham risk scoring. A major study published in JAMA by the Emerging Risk Factors Collaboration reviewed individual records from 37 prospective studies containing 165,544 people without CVD at baseline (19). The study compared traditional lipids to additional measures, including apolipoproteins B and A–I, lipoprotein(a), and lipoprotein-associated phospholipase A2 in individuals followed for a mean of 10 years. Those with CVD events during the study period were analyzed to determine if the alternative markers added significant predictive value. In an accompanying editorial, lipid expert Dr. Scott Grundy concluded that “apolipoproteins are of limited value in reclassifying individuals among arbitrary risk categories, i.e., low-risk, intermediate-risk, and high-risk” (20). Even when a particular test has been shown to add incremental improvement in predicting risk, there has not been sufficient evidence to use the test as a widespread screening tool. Most often, novel risk factors are useful for the patient who has intermediate risk and his/her physician desires additional information to make a decision regarding therapy. It should be considered that, for many novel risk markers, statin therapy does not reduce the marker levels (21) and evidence that treating the specific marker has any real impact on CVD is lacking. For example, it has been shown in multiple meta-analyses that folic acid reduces homocysteine, but does not reduce CVD hazard. Moreover, the various tests available add cost, may add risk (e.g. radiation for imaging) and many of the assays have not been widely standardized, thus resulting in difficulty interpreting the results. Based on current evidence, it is difficult to recommend these alternative risk markers for screening or for routine clinical use and they are probably most appropriate in carefully considered individual cases. However, this topic is an area of intense focus and ongoing research, so future studies may help elucidate a more clearly defined role for novel risk markers.

Treatment goals

A portion of the current treatment goals as outlined by the NCEP/ATP-III are listed in Box 3. The complete guidelines are available on-line from the National Institutes of Health as a quick reference guide (22). These recommendations are generally accepted by some, but not all, medical specialty organizations. Others advocate for a more aggressive approach.

Regardless of the recommendations, it is useful to consider how successful the medical community has been in meeting guideline goals. A national survey conducted in 2003 (NEPTUNE II) showed 67% of the 4,885 patients with elevated cholesterol achieved their LDL cholesterol treatment goal (23). Data from the National Health and Nutrition Examination Surveys (NHANES) document a steady decline in total cholesterol over several decades so that in 2002 no more than 17% of US adults had a total cholesterol level ≥ 240 mg/dL. More recent data from an identical survey in 2008 show that the Healthy People 2010 goal of an average cholesterol below 200 mg/dL in all adults ages 20 – 74 was met in both men and women by 2008 (24). The obvious problem in monitoring these trends is that the percent of the population at or below goal varies considerably by demographic parameters. Therefore, it is useful for every practice to perform quality studies in its own population to determine how well current guidelines are met and to think innovatively about clinic initiatives that can address suboptimal treatment.

Life style modification is the first step to reduce cholesterol levels. Changes in diet, weight loss and increased exercise are all known to be effective. What is also well known is the difficulty in achieving these goals. There are major limitations in most weight loss studies. For example, weight loss programs show weight reduction reduces both cholesterol and TG but long term almost half of the initial weight loss is regained after 1 year (25). In a recent review of various weight loss diets, the authors concluded that the type of diet is less important than the its palatability and the ease of continuing it long term (26). Given these drawbacks to lifestyle change, it may be prudent to achieve lipid lowering goals by initiating medications sooner rather than later. If life style change goals are achieved, the need for medication can be reassessed.

Pharmaceutical Options

Numerous studies have established that for most patients statins are the preferred medical treatment. Currently in the United States, the Food and Drug Administration has approved six drugs of this class (with some available in immediate or extended release forms). See Table 4. Comparative data show that all of them reduce lipid levels to varying degrees, with atorvastatin and rosuvastatin considered to be the “strong” reducers of LDL. While there are not any trials comparing all of the available statins directly to each other, there are a few head to head comparisons of some of the statins. These are shown in Table 5.

Based on available evidence, there is no compelling reason to choose one statin over another for the usual primary care clinic patient. However, those patients with familial combined hyperlipidemia should probably be started on atorvastatin or rosuvastatin (27). Additionally, it has been shown that the presence of xanthomas in heterozygous familial hyperlipidemia confers additional CVD risk to these patients and specialty opinion should be sought (28).

Alternatives to statins

Although statins have reached the status of preferred treatment for hyperlipidemia, there are reasons to consider other medications. Some physicians feel that monotherapy is preferable, while others believe that low to moderate doses of combinations of drugs produce better LDL-C reduction with fewer side effects. There are times when statin therapy is maximal, but the lipid goals have not been met. Finally, there are situations in which statins are either

contraindicated or not tolerated. A full review of these options is beyond the scope of this paper. A number of studies have looked at comparisons of drug combinations (29). Some of the therapeutic options are listed in Table 6.

Use of complementary products (nutraceuticals, herbs, etc.)

Many people prefer complementary and alternative medicines to pharmaceutical products. They want to use these products because they are less expensive to purchase, don't require a prescription and are considered natural. While there are no studies demonstrating that an alternative product is superior to statins in either lipid or CVD reduction, several reviews have shown modest reduction of plasma lipids with the use of substances such as garlic (30), artichoke leaf extract (31), nuts, plant stanolols, psyllium, soluble fiber, orange juice, and red yeast rice (32). Potential resources to help the interested reader learn more are found at The National Institutes of Health National Center for Complementary and Alternative Medicine official web site (http://nccam.nih.gov/), which contains information that is organized both by product and by health condition. It also has links to systematic reviews and meta-analyses conducted in the last 5 years about specific treatments. Another source is the web site www.naturalstandard.com/. The Natural Standard Research Collaboration is a coalition of medical researchers that conducts and reviews research about natural remedies. They rate products using an evidence based methodology and assign each review a grade (A – F) based on the available scientific evidence. Using traditional medical research sources (e.g. PubMed) it is difficult to find systematic reviews of the evidence for the many natural remedies that have putative benefit in promoting a healthier lipid profile. Those that are available generally show only modest cholesterol lowering. A major deficiency in the study of alternative products is the lack of studies that use hard cardiovascular endpoints instead of a surrogate marker, such as changes in LDL-C. As was learned from the experience with products such as rosiglitazone (33; 34) in people with type 2 diabetes, not all favorable changes in serum lipid characteristics translate into a reduction in CVD events. Thus, any study based solely on lipid lowering as an endpoint may be misleading.

Unanswered questions and current controversies

Despite the overall lowering of mean LDL-C and the overall incidence of CVD in the US population, CVD remains a significant health burden and a leading cause of mortality. There remain many unanswered questions and controversies regarding how best to further decrease these numbers. These questions are important because of the expected increase in CVD given the aging population and the obesity epidemic. These are addressed in this section in no particular order.

One of the potential reasons for continuing high rates of CVD is that the target LDL-C goals may be too modest. There are investigators and practitioners who advocate lowering LDL-C as low as can be achieved, possible even to levels < 50 mg/dL. Others argue that the evidence to support this view has not been conclusively shown.

A meta-analysis of trials with cardiovascular outcomes looked at 27,548 patients enrolled in 4 large studies. The authors concluded that high dose statins were significantly better than moderate dose, primarily by reducing non-fatal cardiac events. However, they did not find a statistically significant difference between CV or all cause mortality (35) Another study that showed evidence of improved outcome from high dose statins is the ASTEROID study (36). The investigators used intravascular ultrasound to document atheroma regression after treatment with 40 mg daily of rosuvastatin. The average LDL-C achieved was ~ 60 mg/dL. The study authors concluded that lowering LDL-C below current recommended guidelines can cause regression of atherosclerosis in coronary disease patients. A third major study was

the Treat to New Targets (37). It found that lowering LDL-C to 80 mg/dL in the treatment group was superior in preventing CVD outcomes than lowering it to 100 mg/dL.

Another controversy regarding LDL-C target is the question of how best to achieve the desired goals. One side of the debate advocates high dose statins while the other prefers combination therapy in moderate doses. The question is based in part on a balance between benefit and risk. Statins are known to have beneficial effects in addition to lipid lowering. These pleiotropic effects include antiinflammatory action and improvement in coagulability. The long term risks of the statins are not fully known. There has been recent controversy over the question of whether statins cause type 2 diabetes (38; 39). In addition, there are questions about a possible link of statins to pancreatitis although a recent review disputes this claim (40). A number of the studies that have compared adjunctive therapy consisting of a statin plus another lipid lowering drug with mono-statin treatment are reviewed in an exhaustive report from the Agency for Healthcare Research and Quality (41) Table 7 is a reproduction from the executive summary of the report. The main conclusion of the report is that there is insufficient evidence (especially morbidity/mortality data) to answer the question if high dose monotherapy is different from combination therapy. Currently, there is no definitive answer to the question and each physician needs to make the decision based on incomplete data and a rational balance of risk vs benefit for each individual patient.

A significant unresolved problem in current medical practice is the issue of residual risk. Because a significant number of cases of CVD occur in people without traditional risk factors, some physicians have suggested that nontraditional biomarkers be used to identify those who are at increased risk for CVD despite normal lipid profiles. As previously discussed in the section on novel risk factors, there are no biomarkers that have been convincingly shown by large clinical trials or meta-analysis to be superior to current practice. Despite the scant evidence linking reduction of these markers to reduced incidence of CVD events, some believe cholesterol drugs should be used in healthy people with low probability of CVD (42). This study is cited as an example of the type of analysis that leads some to argue for a more extensive use of statins because there was a significant decrease in CVD events. Others feel this liberal use of statins may constitute unacceptable risk in truly low risk subjects. In the study cited above, the number needed to treat to prevent a single death from any cause and to prevent a single nonfatal myocardial infarction was 239 and 153, respectively. Another approach to addressing residual risk is use of pharmacological means to raise HDL-C. This idea has been challenged by recent trials that failed to show any lowering of CVD events despite raising HDL-C (43; 44). A recently published trial comparing genetic mutations that confer high HDL versus low HDL has called into question the well established belief that HDL-C protects against CVD (45). A third approach to addressing the problem of residual risk has been to focus on TGRL as potential atherogenic agents. The idea is that lowering TG concentrations that are currently recognized as high, but not sufficiently so to treat pharmacologically (i.e. 250 – 499 mg/dL), can have a major impact on CVD. However, recent trials in patients with type 2 diabetes treated with fibrates or niacin have created doubt about this hypothesis (46; 47). Current research is re-examining some of the long held beliefs about the role of various lipid fractions in the etiology of CVD. This work includes both examination of the biochemical pathways in order to identify new potential drug targets and a detailed analysis of the negative studies to determine if the entire idea is wrong or just a portion.

To summarize, there is a solid link between elevated cholesterol (especially LDL-C) and CVD. It has been conclusively shown and become accepted practice to lower LDL-C in patients considered intermediate to high risk for CVD with a combination of therapeutic life style change and medications. First line drug therapy should be a statin, titrated to keep LDL-C at or below the target range recommended by the ATP-III guidelines. Multiple

alternatives are available for those who either are statin intolerant or who fail to achieve therapeutic goals. While these statements are relatively simple, it took decades for them to become standard medical practice. Considerable work is ongoing to identify what factors are most important to residual risk. This work plus ongoing effectiveness research in clinical practice networks should lead to significant changes in how practitioners approach dyslipidemia over the next 1 – 2 decades.

Acknowledgments

Funding sources:

NIDDK (DK82473), No industry funding

REFERENCES

1. National Ambulatory Medical Care Survey: 2009 Summary Tables. National Ambulatory Medical Care Survey: 2009 Summary Tables. The Ambulatory and Hospital Care Statistics Branch of the Centers for Disease Control and Prevention's National Center for Health Statistics, 2009, p. Table 16. Presence of selected chronic conditions at office visits, by patient age and sex: United States 2009; Available at: http://www.cdc.gov/nchs/data/ahcd/namcs_summary/2009_namcs_web_tables.pdf
2. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002; 106:3143–3421. [PubMed: 12485966]
3. Murphy, SL.; Xu, JQ.; KD, K. Deaths: Preliminary data for 2010. National vital statistics reports, Table B. Hyattsville, MD: National Center for Health Statistics; 2012.
4. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA. 1984; 251:351–364. [PubMed: 6361299]
5. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA. 1984; 251:365–374. [PubMed: 6361300]
6. Steinberg D. Thematic review series: the pathogenesis of atherosclerosis. An interpretive history of the cholesterol controversy: part I. J Lipid Res. 2004; 45:1583–1593. [PubMed: 15102877]
7. Steinberg D. Thematic review series: the pathogenesis of atherosclerosis. An interpretive history of the cholesterol controversy: part II: the early evidence linking hypercholesterolemia to coronary disease in humans. J Lipid Res. 2005; 46:179–190. [PubMed: 15547293]
8. Steinberg D. Thematic review series: the pathogenesis of atherosclerosis: an interpretive history of the cholesterol controversy, part III: mechanistically defining the role of hyperlipidemia. J Lipid Res. 2005; 46:2037–2051. [PubMed: 15995167]
9. Steinberg D. The pathogenesis of atherosclerosis. An interpretive history of the cholesterol controversy, part IV: the 1984 coronary primary prevention trial ends it--almost. J Lipid Res. 2006; 47:1–14. [PubMed: 16227628]
10. Steinberg D. Thematic review series: the pathogenesis of atherosclerosis. An interpretive history of the cholesterol controversy, part V: the discovery of the statins and the end of the controversy. J Lipid Res. 2006; 47:1339–1351. [PubMed: 16585781]
11. U.S. Preventive Services Task Force. Screening for Lipid Disorders in Adults. 2008 Available at: http://www.uspreventiveservicestaskforce.org/uspstf/uspschol.htm.
12. American Heart Association. Public Cholesterol Screening. 2011 Available at: http://www.heart.org/HEARTORG/Conditions/Cholesterol/SymptomsDiagnosisMonitoringofHighCholesterol/Public-Cholesterol-Screening-Adults-and-Children_UCM_305617_Article.jsp.
13. Semenkovich, CF.; Goldberg, AC.; Goldberg, IJ. Disorders of Lipid Metabolism. In: Melmed, S.; Polonsky, KS.; Larsen, PR.; Kronenberg, HM., editors. Williams Textbook of Endocrinology, 12th ed. W.B. Saunders; 2011.

14. Aberg JA. Lipid management in patients who have HIV and are receiving HIV therapy. Endocrinol Metab Clin North Am. 2009; 38:207–222. [PubMed: 19217520]
15. Cooper, A.; Nherera, L.; Calvert, N.; O'Flynn, N.; Turnbull, N.; Robson, J.; Camosso-Stefinovic, J.; Rule, C.; Browne, N.; Ritchie, G.; Stokes, T.; Mannan, R.; Brindle, P.; Gill, P.; Gujral, R.; Hogg, M.; Marshall, T.; Minhas, R.; Pavitt, L.; Reckless, J.; Rutherford, A.; Thorogood, M.; D, W., editors. Clinical Guidelines and Evidence Review for Lipid Modification: cardiovascular risk assessment and the primary and secondary prevention of cardiovascular disease. London, England: National Collaborating Centre for Primary Care and Royal College of General Practitioners; 2008. Chapter 3.3 Assessment of cardiovascular risk.
16. Peters SA, den Ruijter HM, Bots ML, Moons KG. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. Heart. 2012; 98:177–184. [PubMed: 22095617]
17. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA. 2012; 308:788–795. [PubMed: 22910756]
18. Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, Simes RJ, Durrington P, Hitman GA, Welch KM, DeMicco DA, Zwinderman AH, Clearfield MB, Downs JR, Tonkin AM, Colhoun HM, Gotto AM Jr, Ridker PM, Kastelein JJ. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. JAMA. 2012; 307:1302–1309. [PubMed: 22453571]
19. Di Angelantonio E, Gao P, Pennells L, Kaptoge S, Caslake M, Thompson A, Butterworth AS, Sarwar N, Wormser D, Saleheen D, Ballantyne CM, Psaty BM, Sundstrom J, Ridker PM, Nagel D, Gillum RF, Ford I, Ducimetiere P, Kiechl S, Koenig W, Dullaart RP, Assmann G, D'Agostino RB Sr, Dagenais GR, Cooper JA, Kromhout D, Onat A, Tipping RW, Gomez-de-la-Camara A, Rosengren A, Sutherland SE, Gallacher J, Fowkes FG, Casiglia E, Hofman A, Salomaa V, Barrett-Connor E, Clarke R, Brunner E, Jukema JW, Simons LA, Sandhu M, Wareham NJ, Khaw KT, Kauhanen J, Salonen JT, Howard WJ, Nordestgaard BG, Wood AM, Thompson SG, Boekholdt SM, Sattar N, Packard C, Gudnason V, Danesh J. Lipid-related markers and cardiovascular disease prediction. JAMA. 2012; 307:2499–2506. [PubMed: 22797450]
20. Grundy SM. Use of emerging lipoprotein risk factors in assessment of cardiovascular risk. JAMA. 2012; 307:2540–2542. [PubMed: 22797454]
21. Balk EM, Lau J, Goudas LC, Jordan HS, Kupelnick B, Kim LU, Karas RH. Effects of statins on nonlipid serum markers associated with cardiovascular disease: a systematic review. Annals of Internal Medicine. 2003; 139:670–682. [PubMed: 14568856]
22. ATP III At-A-Glance: Quick Desk Reference 2001. Available at: http://www.nhlbi.nih.gov/guidelines/cholesterol/dskref.htm
23. Davidson MH, Maki KC, Pearson TA, Pasternak RC, Deedwania PC, McKenney JM, Fonarow GC, Maron DJ, Ansell BJ, Clark LT, Ballantyne CM. Results of the National Cholesterol Education (NCEP) Program Evaluation ProjecT Utilizing Novel E-Technology (NEPTUNE) II survey and implications for treatment under the recent NCEP Writing Group recommendations. Am J Cardiol. 2005; 96:556–563. [PubMed: 16098311]
24. Center for Disease Control and Prevention. Atlanta: U.S. Department of Health and Human Services; 2009. QuickStats: Average Total Cholesterol Level Among Men and Women; p. 1045
25. Curioni CC, Lourenco PM. Long-term weight loss after diet and exercise: a systematic review. Int J Obes (Lond). 2005; 29:1168–1174. [PubMed: 15925949]
26. Makris A, Foster GD. Dietary approaches to the treatment of obesity. Psychiatr Clin North Am. 2011; 34:813–827. [PubMed: 22098806]
27. Hemphill LC. Familial hypercholesterolemia: Current treatment options and patient selection for low-density lipoprotein apheresis. Journal of Clinical Lipidology. 2010; 4:346–349. [PubMed: 21122676]
28. Oosterveer DM, Versmissen J, Yazdanpanah M, Hamza TH, Sijbrands EJ. Differences in characteristics and risk of cardiovascular disease in familial hypercholesterolemia patients with and without tendon xanthomas: a systematic review and meta-analysis. Atherosclerosis. 2009; 207:311–317. [PubMed: 19439299]

29. Sharma M, Ansari MT, Abou-Setta AM, Soares-Weiser K, Ooi TC, Sears M, Yazdi F, Tsertsvadze A, Moher D. Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia. Ann Intern Med. 2009; 151:622–630. [PubMed: 19884623]
30. Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolemia. A meta-analysis of randomized clinical trials. Ann Intern Med. 2000; 133:420–429. [PubMed: 10975959]
31. Wider B, Pittler MH, Thompson-Coon J, Ernst E. Artichoke leaf extract for treating hypercholesterolaemia. Cochrane Database Syst Rev. 2009 CD003335.
32. Nies LK, Cymbala AA, Kasten SL, Lamprecht DG, Olson KL. Complementary and alternative therapies for the management of dyslipidemia. Ann Pharmacother. 2006; 40:1984–1992. [PubMed: 17047144]
33. Nissen SE, K W. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007; 356:2457–2471. [PubMed: 17517853]
34. Jonas, D.; Van Scoyoc, E.; Gerrald, K.; Wines, R.; Amick, H.; Triplette, M.; Runge, T. Drug Class Review: Newer Diabetes Medications, TZDs, and Combinations: Final Original Report [Internet]. Oregon Health &Science University, Portland, OR. 2011. Available from: http://www.ncbi.nlm.nih.gov/books/NBK54209/
35. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol. 2006; 48:438–445. [PubMed: 16875966]
36. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart JC, Tardif JC, Schoenhagen P, Crowe T, Cain V, Wolski K, Goormastic M, Tuzcu EM. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006; 295:1556–1565. [PubMed: 16533939]
37. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005; 352:1425–1435. [PubMed: 15755765]
38. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJM, Seshasai SRK, McMurray JJ, Freeman DJ, Jukema JW, Macfarlane PW, Packard CJ, Stott DJ, Westendorp RG, Shepherd J, Davis BR, Pressel SL, Marchioli R, Marfisi RM, Maggioni AP, Tavazzi L, Tognoni G, Kjekshus J, Pedersen TR, Cook TJ, Gotto AM, Clearfield MB, Downs JR, Nakamura H, Ohashi Y, Mizuno K, Ray KK, Ford I. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. The Lancet. 375:735–742.
39. Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, DeMicco DA, Barter P, Cannon CP, Sabatine MS, Braunwald E, Kastelein JJ, de Lemos JA, Blazing MA, Pedersen TR, Tikkanen MJ, Sattar N, Ray KK. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011; 305:2556–2564. [PubMed: 21693744]
40. Preiss D, Tikkanen MJ, Welsh P, Ford I, Lovato LC, Elam MB, LaRosa JC, DeMicco DA, Colhoun HM, Goldenberg I, Murphy MJ, MacDonald TM, Pedersen TR, Keech AC, Ridker PM, Kjekshus J, Sattar N, McMurray JJ. Lipid-modifying therapies and risk of pancreatitis: a meta-analysis. JAMA. 2012; 308:804–811. [PubMed: 22910758]
41. Sharma, M.; Ansari, MT.; Soares-Weiser, K.; Abou-setta, AM.; Ooi, TC.; Sears, M.; Yazdi, F.; Tsertsvadze, A.; D, M. Comparative Effectiveness Review. Rockville, MD: Agency for Healthcare Research and Quality; 2009. Comparative Effectiveness of Lipid-Modifying Agents. Prepared by the University of Ottawa Evidence-based Practice Center under contract No. 290-02-0021 to Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm
42. Conly J, Clement F, Tonelli M, Hemmelgarn B, Klarenbach S, Lloyd A, McAlister FA, Husereau D, Wiebe N, Au F, Manns B. Cost-effectiveness of the use of low- and high-potency statins in people at low cardiovascular risk. CMAJ. 2011; 183:E1180–E1188. [PubMed: 21989469]
43. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011; 365:2255–2267. [PubMed: 22085343]
44. Ghosh RK, Ghosh SM. Current status of CETP inhibitors in the treatment of hyperlipidemia: an update. Curr Clin Pharmacol. 2012; 7:102–110. [PubMed: 22432840]

45. Voight BF, Peloso GM, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet. 2012; 380:572–580. [PubMed: 22607825]

46. Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC Jr, Cushman WC, Simons-Morton DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010; 362:1563–1574. [PubMed: 20228404]

47. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesaniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005; 366:1849–1861. [PubMed: 16310551]

48. Gregson J, Stirnadel-Farrant HA, Doobaree IU, Koro C. Variation of lipoprotein associated phospholipase A2 across demographic characteristics and cardiovascular risk factors: A systematic review of the literature. Atherosclerosis. 2012

49. Nordestgaard BG, Chapman MJ, Ray K, Boren J, Andreotti F, Watts GF, Ginsberg H, Amarenco P, Catapano A, Descamps OS, Fisher E, Kovanen PT, Kuivenhoven JA, Lesnik P, Masana L, Reiner Z, Taskinen MR, Tokgozoglu L, Tybjaerg-Hansen A. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. 2010; 31:2844–2853. [PubMed: 20965889]

50. Teramoto T. The clinical impact of pitavastatin: comparative studies with other statins on LDL-C and HDL-C. Expert Opin Pharmacother. 2012; 13:859–865. [PubMed: 22332608]

51. Maruyama T, Takada M, Nishibori Y, Fujita K, Miki K, Masuda S, Horimatsu T, Hasuike T. Comparison of preventive effect on cardiovascular events with different statins. -The CIRCLE study. Circ J. 2011; 75:1951–1959. [PubMed: 21673458]

52. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, Raichlen JS, Uno K, Borgman M, Wolski K, Nissen SE. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med. 2011; 365:2078–2087. [PubMed: 22085316]

Key Points

1. Elevated levels of blood lipids are well documented risk factors for cardiovascular disease. Current classification schemes and treatment levels for hyperlipidemia are based on the National Cholesterol Education Panel's (NCEP) Adult Treatment Program-3 (ATP-III) guidelines.
2. Statins are the preferred class of drugs to lower elevated low density lipoprotein cholesterol (LDL-C). There are other classes to augment or substitute for statins, such as ezetimibe, fibrates, niacin and dietary supplements.
3. Extensive research over the last decade has raised the question whether or not ATP-III guidelines are sufficiently aggressive. New guidelines from ATP-IV are expected to be released in the near future, but in the meantime physicians are faced with uncertainty about how low to target LDL-C, whether to pharmacologically treat high density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels and how best to achieve target goals.

Box 1. Classes of Apolipoproteins

- Chylomicrons – Triglyceride rich carrier of dietary fats
- Very Low Density Lipoprotein (VLDL) – Triglyceride rich carrier of hepatic synthesized triglycerides (TG)
- Intermediate and Low Density Lipoprotein (IDL & LDL) – Cholesterol rich remnant particles derived from lipolysis of triglycerides in VLDL
- High Density Lipoprotein (HDL) – Cholesterol rich particle that transports cholesterol to liver for disposal or recycling

Box 2. Recommendations of the US Preventative Services Task Force 2008

- Screen men aged 35 and older (Grade A Recommendation)
- Screen men aged 20 to 35 if they are at increased risk for coronary heart disease* (Grade B Recommendation)
- Screen women aged 45 and older if they are at increased risk for coronary heart disease. (Grade A Recommendation)
- Screen women aged 20 to 45 if they are at increased risk for coronary heart disease. (Grade B Recommendation)
- No recommendation for or against routine screening men aged 20 to 35, or in women aged 20 and older who are not at increased risk for coronary heart disease. (Grade C Recommendation)

*Increased risk for CVD is defined by risk factors. These include men with diabetes, a family history of heart disease in a close male relative younger than age 50 or a close female relative younger than age 60, a family history of high cholesterol, or a personal history of multiple coronary disease risk factors (e.g., smoking, high blood pressure).

Box 3. Summary of some novel or alternative risk factors with recommendations for their use based on different sources

• CRP	Recommended for routine measurement in intermediate risk subjects
• Lp-PLA2	Consider for selected patients
• Apo-B	Reasonable for many intermediate risk patients
• LDL-P	Reasonable for many intermediate risk patients
• Lp(a)	Consider for selected patients
• LDL Subfractions	Not Recommended
• HDL Subfractions	Not Recommended

Journal of Clinical Lipidology (2011) 5:338

- Imaging (Carotid intima thickening, coronary artery calcium by CT)
  Primary value is asymptomatic individuals at intermediate cardiovascular risk. Further research is recommended

Heart (2012) 98:177e184

• Fibrinogen.	Not Recommended (effective treatment not demonstrated)

Heart (2006) 92:166

• homocysteine	Not Recommended (effective treatment not demonstrated)

PLoS ONE, (2011) 6:e25142

Box 4. Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for Three Risk Categories based on ATP-III guidelines*

If CVD 10 year risk is:

- > 20%, then LDL < 100 and non-HDL < 130
- ≤20% plus 2 or more risk factors, then LDL < 130and non-HDL < 160
- 0–1 risk factors, then LDL < 160 and non-HDL < 190

* ATP-4 guidelines are expected this year and will probably significantly change these recommendations.

Table 1

Classification of hyperlipidemias as defined by the NCEP ATP 3. All concentrations are expressed as mg/dL

LDL Cholesterol	
<100	Optimal
100 – 129	Near or above optimal
130 – 159	Borderline high
160 – 189	High
≥ 190	Very high
Total Cholesterol	
<200	Desirable
200 – 239	Borderline high
≥ 240	High
HDL Cholesterol*	
<40	Low
≥ 60	High
Triglycerides	
<150	Normal
150 – 199	Borderline high
200 – 499	High
≥ 500	Very high

Table 2

Genetic causes of hyperlipidemia (13)

CAUSES	CLINICAL FEATURES
Isolated cholesterol elevation	
Genetic Familial Hypercholesterolemia	relatively common (1 in 500 heterozygote); TC exceeds 300 mg/dL, family history of elevated TC common, associated with tendon xanthomas, premature (20 – 40 years old) CVD is common Homozygotes are rare, but have TC > 600 and if not treated usually die of MI prior to age 20.
Familial Defective Apolipoprotein B100	increases LDL and has a phenotype that is indistinguishable from that of FH, including increased susceptibility to CHD
Mutations Associated with Elevated LDL Levels	Rare and isolated; suspect if elevated LDL unresponsive to treatment
Elevated Plasma Lipoprotein(a)	Relationship to CVD unclear, studies contradictory (48; 49)
Polygenic Hypercholesterolemia	No family history, no physical manifestations such as xanthomas, exact cause is unknown
Lp(X)	Associate with obstructive hepatic disease, CVD risk unclear
Sitosterolemia	rare; plant sterols absorbed in large amounts, tendon xanthomas develop in childhood, LDL levels normal to high
Cerebrotendinous Xanthomatosis	rare; associated with neurologic disease, tendon xanthomas, and cataracts in young adults
Elevated cholesterol and triglycerides	
Combined (Familial) Hyperlipidemia	May occur randomly or with strong family history of hyperlipidemia; type 2 diabetes and metabolic syndrome are associated and can make diagnosis more difficult
Familial Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)	severe hypertriglyceridemia and hypercholesterolemia (both often > 300), associated with premature diffuse vascular disease, male predominance, Palmar xanthomas are pathognomonic
Hepatic Lipase Deficiency	Rare disorder with very high cholesterol and triglyceride concentrations, phenotypically similar to familial dysbetalipoproteinemia.
Isolated triglyceride elevations	
LPL deficiency	Results in elevated chylomicrons, which carry dietary fat; chylomicrons are generally not present after an overnight fast, so a creamy looking plasma in a fasting specimen should be a clue to the diagnosis, especially if seen in young children; extremely high triglycerides can lead to pancreatitis
ApoCII deficiency	This apolipoprotein is an activator of LPL; its absence causes a clinical picture identical to LPL deficiency
Familial hypertriglyceridemia	Autosomal dominant inheritance; Main defect is overproduction of VLDL triglycerides by the liver;

Table 3

Secondary causes of hyperlipidemia

Diet	**Drugs**	**Disease & Disorders of Metabolism**
Saturated & *trans* Fats	Thiazide Diuretics	Hypothyroidism
Excess Calories	Beta-Blockers	Obesity
Alcohol	Glucocorticoids	Type 2 Diabetes
Red meat	Sex hormones	Metabolic syndrome
Whole milk	Retinoic Acid derivations	Renal disease
High sugar beverages & foods	Antipsychotics	HIV
	Antiretrovirals	PCOS
	Immunosuppressive agents	

Table 4

Current HMG-CoA-inhibitors.

Drug	Trade Name	Dose Range	% LDL-C Decrease	% HDL-C Increase	% TG Decrease
Fluvastatin	Lescol	20–80 mg	22–35	3–11	17–21
Pravastatin	Pravachol	10–80 mg	22–37	2–12	15–24
Lovastatin	Altoprev/Mevacor	10–80 mg	21–42	2–8	6–21
Simvastatin	Zocor	5–80 mg	26–47	10–16	12–33
Atorvastatin	Lipitor	10–80 mg	39–60	5–9	19–37
Rosuvastatin	Crestor	5–40 mg	45–63	8–10	10–30
Pitavastatin	Livalo	1–4 mg	38–44	5–8	14–22

Table 5

Studies of direct comparisons of 2 or more statins' efficacy in lipid lowering.

Study Name	Number Participants	Drugs Compared	Conclusions
*PATROL (50)	302	pitavastatin, atorvastatin, and rosuvastatin	The safety and efficacy of these 3 strong statins are equal
**CIRCLE (51)	743	atorvastatin vs pitavastatin vs pravastatin	Pitavastatin or atorvastatin resulted in better reduction of LDL-C than pravastatin; pitavastatin significantly increased HDL-C compared to placebo, while the other two statins did not
*SATURN (52)	1039	atorvastatin vs rosuvastatin	No difference in progression of arterial plaques by intravascular ultrasound despite statistically significant lower LDL with rosuvastatin

* prospective randomized multi-center trial,

** Retrospective study.

Table 6

Statin alternatives

DRUG	EFFECTS	ADVERSE REACTIONS
Bile acid sequestrants		
Cholestyramine (4–16 g) Colestipol (5–20 g) Colesevelam (2.6–3.8 g)	LDL −15–30% HDL +3–5% TG No change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs
Nicotinic acid		
Immediate release (crystalline) nicotinic acid (1.5–3 gm), extended release nicotinic acid (Niaspan®) (1–2 g), sustained release nicotinic acid (1–2 g)	LDL −5–25% HDL +15–35% TG −20–50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity
Fibric acids		
Gemfibrozil (600 mg BID) Fenofibrate (200 mg) Clofibrate(1000 mg BID)	LDL −5–20% (may be increased in patients with high TG) HDL +10–20% TG −20–50%	Dyspepsia Gallstones Myopathy
Ezetimibe		
Zetia (10 mg daily) As monotherapy, often combined with a statin	LDL-C −18% HDL-C +3% TG −8%	Diarrhea Arthralgia Nasopharyngitis or Sinusitis Controversial regarding reduction of CVD events
Omega 3 fatty acids		
Lovaza Fish Oil Plant sources	Prescription fatty acid ester indicated only for treatment of TG > 500 mg/dl to prevent pancreatitis Fish oil has been shown to reduce elevated TG with subsequent mild reduction in LDL and non-HDL-C; however a recent major study showed no benefit from fish oil capsules; consumption of fish is preferred. Plant sources of omega-3 FA have been subjected to few clinical trials with CVD endpoints	

Table 7

Summary of conclusions from evidence comparing use of a specific statin in combination with another lipid-modifying agent with use of a higher dose statin in populations requiring intensive treatment and subgroups

Outcome	Strength of Evidence (GRADE)	Summary/conclusions
Key Question 1. 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) compared with higher dose statin monotherapy?		
All-cause mortality	Very low	Insufficient evidence was available regarding mortality. Based on small trials with few events, no difference in mortality was noted for any statin combination associated with ezetimibe or fibrates compared with higher dose statin monotherapy. No evidence was available for other combinations.
Vascular death	---	No evidence was available for any statin combination vs. higher dose statin monotherapy.
Serious[a] adverse events	Very low	Up to a maximum followup of 24 weeks, no intervention was significantly safer when statin-ezetimibe combination was compared with higher dose statin monotherapy. No evidence was available for other combinations.
Key Question 2. Do these regimens differ in reaching LDL targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?		
Attainment of ATP III LDL-c goals	Very low	Ezetimibe plus simvastatin therapy is more likely to result in attainment of LDL-c target than higher dose simvastatin, based on 2 small trials. Results for statin-fibrate combination (1 trial) were indeterminate. No evidence was available for other combinations.
Key Question 3. Compared with higher dose statins and to one another, do combination regimens differ in benefits and harms within subgroups of patients?		
All-cause mortality, vascular death, and attainment of ATP III LDL-c goals	Very low	There is insufficient evidence to draw any meaningful conclusions in subgroups for any combination.
Serious adverse events	---	Since absent to scant subgroup evidence was anticipated, SAE was examined across all trial populations (see above).
Inter-combination, indirect comparison of syntheses		We are unable to confirm a difference in benefits or harms between combinations due to the lack of evidence.

[a]Because of scant evidence for those in need of intensive lipid lowering, SAE was examined across all trial populations

Abbreviations: ATP III=Adult Treatment Panel III (of the National Cholesterol Education Program); GRADE=Grading of Recommendations Assessment, Development and Evaluation; LDL-c=low-density lipoprotein cholesterol; SAE=serious adverse events.