Draft Comparative Effectiveness Review
Number XX (Provided by AHRQ)

Comparative Effectiveness of Lipid Modifying Agents

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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Appendices

See separate attachment (Appendices A-F)

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Comparative Effectiveness of Lipid Modifying Agents
Executive Summary

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at
www.effectivehealthcare.ahrq.gov/reports/final.cfm

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Background

Over 28 million Americans have some form of cardiovascular disease (CVD), and these conditions cause more deaths than cancer, diabetes, accidents and chronic lung diseases combined. Direct medical expenditures and lost productivity due to CVD cost an estimated $431.8 billion in the United States in the year 2007.

Only one third of patients achieve their LDL-c goals, proportionally even fewer with established CHD. Current statin therapy leads to moderate LDL-c reductions. Alternatives for dyslipidemic patients include dose titration, combination therapy or prescribing a more efficacious statin. This review examines evidence of health benefits and harms of combination therapies compared with statin monotherapy in those in requiring of intensive lipid lowering.

As early as 1961, the American Heart Association recognized that cholesterol was causally linked to CHD and advised that people at high risk modify their diets. The first large trial demonstrating a reduction in cardiac endpoints with lowering of cholesterol levels was the Coronary Primary Prevention trial, funded by NIH and published in 1984. The era of potent lipid modifying therapies was ushered in by the 4S Trial, which demonstrated a 42% reduction in CHD mortality and a reduction in all cause mortality following treatment with simvastatin. In addition, the National Cholesterol Education Program (NCEP) was established, and published its first report in 1988. The NCEP guidelines have been updated, with the most recent full report published in 2002 as the Adult Treatment Panel III (ATP III).

Trial evidence suggests that lowering LDL-c reduces incidence of CHD and ischemic stroke. Due to the consistent and robust association of higher LDL-c levels with disease across experimental and epidemiologic studies, therapeutic strategies have focused on LDL-c reduction as the primary goal. The ATP III report established three risk strata for CHD with upper LDL-c thresholds for the initiation of treatment, and therapeutic LDL-c targets. The highest risk individuals were defined as those with established CHD or CHD risk equivalents (i.e. diabetes,

clinical atherosclerotic disease in other vascular beds, or multiple (2+) risk factors resulting in a CHD ten year risk of more than 20%).

The 2002 risk stratification expanded the population for whom lipid modifying therapy was recommended, and subsequently five major trials led to a NCEP ATP III revision in 2004. These additions to the evidence base confirmed the inclusion of diabetes as a CHD risk equivalent and reinforced the benefits of LDL-c lowering in older individuals. In addition, for very high risk individuals, more aggressive targets were felt to be a therapeutic option. The previous target of LDL-c < 100 mg/dL was supplemented with an optional goal of LDL-c < 70 mg/dL in very high risk populations. Very high risk individuals 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 of the metabolic syndrome. High risk patients continued to be defined as in ATP III. While the optional target of LDL-c < 70 mg/dL was supported by two of the trials reviewed by NCEP, further trial confirmation was sought prior to considering this definitive. Finally, ATP III suggests that individuals without established disease or multiple risk factors but an LDL-c > 190 mg/dL should be treated to a target LDL-c of 160 mg/dL.

A number of medications are available for lipid modifying therapy. The most widely prescribed agents are the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors commonly known as statins. HMG-CoA reductase is the rate limiting enzyme for cholesterol synthesis in the liver. Statins are structural analogues of HMG-CoA, competitively binding to the reductase enzyme. In addition, statins reduce plasma cholesterol by upregulation of the LDL-c receptor, leading to uptake of LDL-c from the blood. A number of other actions have been noted experimentally including suppression of inflammatory molecules, stimulation of endothelial nitric oxide (eNOS), and inhibition of smooth muscle proliferation and reactive oxygen species. These mechanisms may have a role in the reduction of clinical events, though some debate remains. The older statins (mevastatin, lovastatin, pravastatin, and simvastatin) are fungal metabolites, whereas the newer ones are synthetic (fluvastatin, atorvastatin, and rosuvastatin).

Other lipid modifying agents examined in this review are:

- Fibric acid derivates which reduce the levels of fatty acids in the blood by oxidation of these molecules.
- Ezetimibe, a novel agent which inhibits intestinal absorption by acting on the sterol transporter NPC1L1.
- Niacin (nicotinic acid) which reduces LDL-c and increases HDL-c via a mechanism yet to be fully elucidated.
- Bile acid sequestrants (BAS) that bind bile acids in the bowel, thereby preventing reabsorption of bile from the intestine. The bound bile acids are subsequently excreted in the feces.
- Omega-3 fatty acids have been postulated to have a number of effects of benefit to individuals at risk for vascular disease, including antithrombotic and blood pressure lowering effects. They are considered to be lipid modifying agents due to a reduction in triglycerides, particularly postprandially.

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Therapeutic options for individuals requiring aggressive modification of cholesterol level include increased dose of a statin medication or the use of a statin in combination with a lipid modifying agent of another class.

This report summarizes the evidence for the effectiveness and safety of statins co-administered with one of the non-statin lipid modifying agents listed above.

The following key questions are addressed in this report:

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 co-administration of different lipid-modifying agents (i.e. a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

Key Question 2. Do these regimens differ in reaching LDL-targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

Key Question 3. Compared with higher-dose statins, and to one another, do combination regimens differ in benefits and harms within subgroups of patients

Conclusions

"Low" or "very low" strengths evidence, as assessed using GRADE, were available to draw the conclusions presented on this report. The one exception is a single 5-year study with omega-3 fatty acids in over 18000 participants that rated "moderate," with neutral odds ratio for all-cause mortality in a mixed population.

Few long term studies reported major clinical endpoints, such as incidence of MI, mortality, adverse events and adherence to treatment.

Rather than comparing lower dose statin combination therapy with higher dose monotherapy, the comparator in most trials was the same dose of statin with or without additional lipid modifying medication. Overall, the majority of trials used ezetimibe plus statin combinations.

In summary, the evidence does not support routine use of any studied combination over higher dose statin therapy. A number of questions remain as to the optimal strategies combining efficacy, safety and adherence to treatment for lipid modification in those requiring intensive therapy. Long term trials with clinical outcomes are required to resolve these issues.

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Table A. Summary of conclusions regarding comparative syntheses of statins plus non-statin drug combination therapy compared with statin monotherapy

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 co-administration 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 impact was noted for omega-3 fatty acids, ezetimibe and fibrates on mortality. No evidence for the other agents.
Vascular death	very low	No evidence was available for any combination.
Serious adverse events	very low	Combination therapies do not demonstrate an increase in adverse events over statin monotherapy. Ezetimibe studies are of sort duration while all other agents have limited numbers of studies and participants.
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	low	Ezetimibe plus simvastatin therapy is more likely to result in attainment of LDL-c target than higher dose simvastatin, based on two small trials.
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	very low	No benefit or harm is noted for any combination in any subgroup. There is insufficient data on ethnic origin for all therapies apart from one large trial demonstrating no impact of omega 3 combination therapy on mortality in an Asian population. There is no data for BAS and niacin for this outcome in any prespecified subgroup.
Vascular death	very low	No benefit or harm for ezetimibe combinations for high risk participants or those with LDL-c above 190 mg/dL, based on one long term trial.
Serious adverse events[7]	low	No increased risk identified based on a limited number of trials most of short duration.
Attainment of ATP III, LDL-c goals[8]	low	Ezetimibe plus statin combination therapy demonstrated a greater probability of goal attainment than any dose statin monotherapy for high risk participants with diabetes and/or established vascular disease. One small trial suggests benefit for those of Hispanic or African descent. Two trials of fibrate combinations are neutral for participants with diabetes mellitus and for all high risk participants. No other evidence is available.
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.

* GRADE was moderate for omega-3 fatty acids. No significant difference was seen, in all participants.
Abbreviations: ATP III = Adult Treatment Panel III (of the NCEP), GRADE = Grading of Recommendations Assessment, Development and Evaluation , LDL-c = low density lipoprotein cholesterol

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Future Research

This review has identified a number of areas requiring future research. Our recommendations address research methodologies in general, and specific needs for research to address key questions

Research methodologies and reporting

All trials must ensure adequate allocation concealment and intention to treat analysis. Blinding and end point adjudication should be employed to minimize bias.

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 co-administration of different lipid-modifying agents (i.e. a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

1. The comparator for trials of combination therapy in which LDL-c reduction or clinical events are a major outcome should be a higher dose statin in most instances. The bulk of the clinical evidence for this endpoint as well as clinical endpoints exists for statin monotherapy. Until a compelling case can be made for a particular combination therapy, comparisons with lower doses of statins are unhelpful.

2. Studies of combination therapy should be conducted over longer time periods and be powered for clinical endpoints. The current evidence base lacks trials of this type, significantly limiting the conclusions which can be drawn.

3. Adverse events should be prospectively collected and comprehensively reported. Short duration trials are unlikely to accrue sufficient adverse events, particularly those with longer latency periods.

4. As the possibility of harm cannot be excluded for some individuals with symptomatic cerebrovascular disease, this population should be specifically studied in order to better define the parameters for those in whom intensive combination therapy is recommended.

5. Concomitant and antecedent therapy should be explicitly stated as both of these factors may influence outcomes. In studies employing a mixture of statin medications and/or doses, results should be reported by medication and dose in order to allow pooling across studies.

6. Studies targeting HDL-c elevation in a population with LDL-c at target are recommended. The absence of such evidence limits the ability to assess the role of combination therapies which raise HDL-c levels.

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Key Question 2: Do these regimens differ in reaching LDL-targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

1. Reporting of surrogate measures should be consistent across all trials. In particular we recommend that the following be included in all reports: attainment of ATP 3 targets, and LDL-c, HDL-c, triglycerides as change scores or post treatment means.

2. The comparator for trials of combination therapy in which LDL-c reduction is major outcome should be a higher dose statin in most instances.

3. Studies to correlate LDL-c with CIMT and clinical outcomes should be conducted in different populations (e.g. participants with diabetes mellitus, CHD, and multiple risk factors as defined by ATP III), with reporting of antecedent therapy as this may be a determinant of outcome.

4. As medication adherence and persistence are important determinants of outcome and are correlated with the complexity of the treatment regimen, studies should be undertaken to compare combinations delivered as a single pill as opposed to two separate ones..

5. Measures of adherence and persistence are affected by the duration of the study period and thus longer term trials are required for combination therapies of lipid modifying agents. A trial duration of greater than 6 months and preferably 1 year is recommended.

Key Question 3: Compared with higher dose statins, and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

1. Trials should be conducted in specific subgroups in order to determine relative benefits and harms. These groups include older individuals, participants with diabetes mellitus and multiple risk factors, and those of African, Hispanic and Asian descent.

2. Trials including women and the groups identified above should report results in a manner amenable to extraction and pooling in order to permit the early identification of a differential effect in specific subgroups.

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Introduction

Background

Over 28 million Americans have some form of cardiovascular disease (CVD) and these conditions cause more deaths than cancer, diabetes, accidents and chronic lung diseases combined.[1] An American dies every 36 seconds as a result of CVD, accounting for 2400 deaths per day.[1] CVD includes coronary heart disease (CHD), heart failure (HF) and stroke. The Framingham Heart Study, an ongoing longitudinal study of CVD and its risk factors, suggests that the lifetime risk of developing disease for those well at age 50 is 51.7% for men and 39.2% for women.[2] Direct medical expenditures and lost productivity as a result of these conditions result in an estimated cost of $431.8 billion in the United States in the year 2007.[3]

Experimental evidence linking cholesterol and vascular disease existed as early as the beginning of the 20th century. In 1913 Nikolai Anitschkow, a Russian experimental pathologist demonstrated that feeding rabbits a diet rich in cholesterol resulted in vascular lesions with the same pathology as those which were known to occur in human atherosclerosis.[4]

Ancel Keys, working at the University of Minnesota, performed one of the earliest epidemiologic studies correlating cholesterol levels with the risk of death from CHD in the Seven Countries study.[5-7] This ecologic study demonstrated a relationship between dietary cholesterol intake, serum cholesterol levels and the CHD death rate of seven populations chosen to represent a range of serum cholesterol. The American Heart Association accepted that cholesterol was causally linked to CHD as early as 1961, and recommended that people at high risk be advised to modify their diets.[4] The first large trial demonstrating a reduction in cardiac endpoints by lowering cholesterol levels was the Coronary Primary Prevention trial, funded by the National Institutes of Health (NIH) and published in 1984.[8] Subsequently the National Cholesterol Education Program (NCEP) was established, with its first report published in 1988.[9] The era of potent lipid lowering therapies was ushered in by the 4S Trial, which demonstrated a 42% reduction in CHD mortality and a reduction in all cause mortality following treatment with simvastatin. The NCEP guidelines have been updated, with the most recent full report published in 2002 as the Adult Treatment Panel III (ATP III).[10]

An understanding of the biology underlying vascular disease has paralleled the development of therapeutic options and guidelines. Atherosclerosis is a pathologic process involving injury to vessel walls with subsequent accumulation of lipids, proteins and inflammatory cells within the wall. Impairment of blood flow due to blockage of the vessel, and promotion of thrombosis or embolization of material into smaller blood vessels result in impaired function or death of tissues.

Cholesterol is transported in the blood as particles combining lipids and proteins called lipoproteins. Low density lipoprotein cholesterol (LDL-c) level in the serum is positively correlated with the development of atherosclerosis, while the levels of high density lipoprotein cholesterol (HDL-c) show an inverse relationship with the atherosclerotic process. The levels of HDL-c are affected by a number of other risk factors including diabetes, obesity and smoking. Guidelines have not identified a level of HDL-c as a goal for therapy, although ATP III does encourage therapies to elevate HDL-c as part of the management strategy.[10] Additionally, elevated serum triglycerides are atherogenic and associated with increased risk for CHD. Therefore, lifestyle modification is recommended for first line therapy in individuals with

elevated triglycerides. The biologic processes and interactions between other lipid fractions and risk factors are complex and beyond the scope of this review.

Trial evidence suggests that lowering of LDL-c results in a reduction in CHD and, recently, rates of ischemic stroke..[11,12] Due to the consistent and robust association of higher LDL-c levels with disease across experimental and epidemiologic studies, therapeutic strategies have focused on LDL-c reduction as the primary goal. The ATP III report established three risk strata for CHD with upper LDL-c cut-off points for the initiation of treatment and therapeutic LDL-c targets. The highest risk individuals were defined as those with established CHD or CHD risk equivalents (i.e. diabetes, clinical atherosclerotic disease in other vascular beds, or multiple (2+) risk factors resulting in a CHD ten year risk of more than 20%). This stratification expanded the population for whom lipid lowering therapy was recommended. Following its publication, five major trials were published resulting in a NCEP ATP III revision in 2004.[13] These additions to the evidence base confirmed the inclusion of diabetes as a CHD equivalent and reinforced the benefits of LDL-c lowering in older individuals. In addition, for very high risk individuals, more aggressive targets were felt to be a therapeutic option. The previous target of LDL-c < 100 mg/dL was supplemented with an optional goal of LDL-c < 70 mg/dL in very high risk populations. The option was also extended to patients at very high risk who already have baseline LDL-c < 100 mg/dL. Very high risk individuals 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 of the metabolic syndrome.[13] High risk patients continued to be defined as in ATP III. While the optional target of LDL-c < 70 mg/dL was supported by two of the reviewed trials,[14,15] further trial confirmation was sought prior to considering this definitive. Finally, ATP III suggests that individuals without established disease or multiple risk factors but an LDL-c > 190 mg/dL should be treated to a target LDL-c of 160mg/dL. This population may also be considered as being in need of intensive lipid lowering if the initial LDL-c is very high.

Cholesterol is a structural component of cellular membranes and acts as a precursor of steroid hormones and bile acids. Cholesterol plasma levels are influenced by production in the liver as well as absorption of ingested fats. Hepatic synthesis of cholesterol begins with 2 carbon acetyl CoA moities which are condensed to hydroxymethylglutaryl CoA (HMG CoA) by HMG CoA synthase. The next step in this metabolic pathway, the conversion of HMG CoA to mevalonate by HMG CoA reductase, has been the chief pharmaceutical target. Dietary cholesterol reaches the liver after absorption in the intestine as chylomicrons which contain triglycerides and cholesterol. The triglycerides are metabolized to fatty acids that are taken up by peripheral tissue, leaving the cholesterol rich particles to be absorbed by the liver. Bile acids, which are critical for absorption of dietary fat and fat soluble vitamins, are produced in the liver and excreted with free cholesterol into the intestine. Approximately 90% of the excreted bile salts are reabsorbed during digestion. Cholesterol is actively absorbed from the intestine by Nieman-Pick C1 Like 1 (NPC1L1), a protein localized in jejunal enterocytes.

A number of medications are available for use as lipid lowering therapy (Table 1). These agents differ in mechanism of action and pharmacokinetic properties.

The most widely prescribed agents are the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors commonly known as statins. These agents are structural analogues of HMG-CoA, the rate limiting enzyme for cholesterol synthesis in the liver, and competitively bind to it. In addition statins reduce plasma cholesterol by upregulating the LDL-c receptor, that

leads to increased uptake of LDL-c from the blood. A number of other actions have been noted experimentally including suppression of inflammatory molecules, stimulation of endothelial nitric oxide (eNOS), and inhibition of smooth muscle proliferation and reactive oxygen species. These mechanisms may have a role in the reduction of clinical events, though some debate remains. The older statins (mevastatin, lovastatin, pravastatin, and simvastatin) are fungal metabolites, whereas the newer ones are synthetic (fluvastatin, atorvastatin, and rosuvastatin). In contrast with statins, fibrates do not influence lipid synthesis but rather reduce the levels of fatty acids in the blood by oxidation of these molecules. Both gemifibrozil and fenofibrate are available for use in the US.

Ezetimibe, is a novel agent which inhibits intestinal absorption by acting on the sterol transporter NPC1L1.[16]Thus combination therapy of a statin and ezetimibe have the potential to influence both the biosynthetic pathway for cholesterol synthesis and absorption.

Niacin (nicotinic acid) reduces LDL-c and increases HDL-c via a mechanism yet to be fully elucidated, though it is suspected to be involved in the metabolism of apolipoproteins. Niacin is thought to stimulate production of ApoA-I and Apo A-II, and may decrease their turnover in addition to decreasing synthesis of LDL-c and VLDL-c without affecting fecal excretion of fats and bile acids.[17,18] This agent was first introduced in 1954 and is available in immediate release and slow release forms but the high prevalence of side effects, chiefly flushing and rash which may occur in up to 60% of individuals have limited usage.[19]

Bile acid sequestrants bind bile acids in the bowel, thereby preventing reabsorption of bile from the intestine. The bound bile acids are subsequently excreted in the feces, thereby preventing reabsorption and depleting the intrahepatic pool of bile acids. They are not absorbed in the intestine and thus do not have systemic side effects. These agents have been available for over thirty years with clinical benefit demonstrated in the Lipid Research Clinics Coronary Primary Prevention Trial.[8] This trial demonstrated a reduction in CAD (coronary heart disease) of approximately 19% in dyslipidemic males with cholestyramine used as monotherapy. Drawbacks of these agents include gastrointestinal side effects, especially constipation, the need for frequent dosing, and the potential to interfere with absorption of other drugs .[20]

Omega-3 fatty acids have been postulated to have a number of effects of benefit to individuals at risk for vascular disease, including antithrombotic and blood pressure lowering effects. They are considered to be lipid modifying agents due to a reduction in triglycerides, particularly postprandially.[21-24] Omega-3 fatty acids come in two forms: the fish oil derived long chain fatty acids, eicosapentaenoic (EPA), docosapentaenoic (DPA) and docosahexaenoic (DHA) ; and the plant oil derived alpha linolenic acid (ALA).Based on a review of the available epidemiologic and trial data the American Heart Association (AHA) nutrition committee has recommended an intake of one gram of EPA+DHA per day for individuals with documented CHD and two to four grams for those in need of triglyceride lowering.[25]

A large number of Americans fall into populations requiring lipid modifying therapy. The populations have been well defined by the ATP III guidelines and recent modifications have served to increase both the number of individuals falling into groups for whom therapy is recomended as well as increasing the intensity of treatment recommended to reach lower targets. Therapeutic options for individuals requiring aggressive lowering of cholesterol include an increased dose of a statin medication or the use of a statin in combination with a lipid modifying agent of another class. The purpose of this review is to compare the benefits and risks of these two options.

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Table 1. Drugs included in the review and label information

Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
HMG-CoA reductase inhibitors (Statins) inhibit conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, an early step in the cholesterol biosynthetic pathway Contraindications: active liver disease; unexplained persistent ↑ transaminases; pregnancy; lactation Withhold therapy if patient is experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.					
Atorvastatin Calcium	Lipitor®	Plasma peak: 1-2 h Biovailability: 14% systemic; 30% Absorption ↓ with food but LDL-c reduction similar regardless of food Highly plasma protein-bound ½-life: Plasma ~14h; Activity 20-30 h Fecal excretion In liver ↓ LDL receptors on the cell-surface ↑ cellular uptake and catabolism of LDL Metabolized by CYP450 3A4	↓ TC, LDL-c, Apo B, and TG levels and ↑ HDL-c in FH, nFH, and mixed dyslipidemia (Types IIa and IIb) ↓ serum TG levels (Type IV) Primary dysbetalipoproteinemia (Type III) ↓ total-C, LDL-C in HoFH‡ ↓ risks of myocardial infarction, stroke, angina, need for revascularization, and hospitalization for congestive heart failure, in CHD Contraindications: ↑ CPK	10, 20, 40, 80 mg tablets Initially 10 mg/d; max 80 mg/d Titrate q 2-4 wks as appropriate May be combined with bile acid sequestrants; maximize time between agents Do not combine with fibrates Ator levels, myopathy and/or rhabdomyelitis risk ↑ with concurrent cyclosporine, fibrates, niacin, CYP450 3A4 substrates§	↑ Cmax, ↑ AUC in people > 65y compared to younger adults ↑ Cmax, ↓AUC in women compared to men (no significant difference in LDL↓) ↑ AUC of concomitant norethindrone and ethinyl estradiol contraceptives

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Drug	Trade name	Pharmacokinetics	Labelled indications* **Contraindications†** (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Fluvastatin sodium or Fluvastatin sodium Extended-Release	Lescol® or Lescol® XL	Plasma Peak Lescol < 1h; Lescol XL ~ 3h Absorption slower but not decreased with food ↑ Cmax, AUC with hepatic insufficiency Highly variable pharmocokinetics [doses > 20mg … enantiomer differences at peak] Highly plasma protein-bound Metabolism by CYP450 2C9; 2C8 and 3A4 to lesser extent Excretion: 90% feces; primarily metabolites	↓ TC, LDL-c, Apo B, and TG levels and ↑ HDL-c in HeFH, nFH, and mixed dyslipidemia (Types IIa and IIb) ↓ need for revascularization procedures, slow coronary atherosclerosis in CHD	20, 40 mg Lescol® capsules and 80 mg Lescol® XL tablets Initial dose 20 mg, titrate q 6-wks as indicated by lipid levels and liver function Interactions: ↑ Fluv Cmax, AUC with cyclosporine ↓ Fluv Cmax, AUC, plasma clearance with Rifampicin ↓ Fluv Cmax, AUC, ↑ plasma clearance with Cimetidine, Ranitidine, Omeprazole ↑ phenytoin and Fluv Cmax and AUC when used concomitantly ↑ Diclofenac Cmax, AUC with Fluv ↑ Glibenclamide (Glyburide) Cmax, AUC, t½, with Fluv – monitor carefully Monitor prothrombin times with warfarin	Renal insufficiency – no adjustment necessary Hepatic insufficiency – caution with history of liver disease or heavy alcohol ingestion

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Drug	Trade name	Pharmacokinetics	Labelled indications* **Contraindications**† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Lovastatin	ALTOCOR™ Extended release	Inactive lactone metabolized to beta-hydroxyacid and further active metabolites Absorption: ~ 30% Excretion: primarily feces; ~10% urine Crosses placenta and blood-brain barrier Highly plasma protein-bound CYP450 3A4 substrates§ ↑ drug exposure, myopathy risks	↓ LDL-C, Total-C, TG; ↑ HDL-C in HeFH, nFH, mixed dyslipidemia (Type IIa, IIb) Less effective, more incidents of ↑ transaminases in HoFH	10, 20, 40, 60 mg tablets 1 tab at bedtime; start low, titrate q 4 wks ≤ 20 mg if taken with niacin ↑ myopathy with fibrates, >1g/day niacin, cyclosporine, CYP450 3A4 substrates§	↓ LDL-C, Total-C, variable ↓ TG, variable ↑ HDL-C drug exposure ↓ with food

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Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Pravastatin sodium	PRAVACHOL®	Drug in active form Elimination ½ life 77 h Highly variable plasma peak and AUC for healthy and cirrhotic subjects Evening dose ↓ systemic bioavailability; ↑ efficacy ~20% plasma protein-bound ~50:50 renal:fecal excretion Not metabolized by CYP450 3A4	↓ risk of MI, need for revascularization, death from cardiac events, with HC, with and without clinically evident CHD ↓ risk of stroke, slow coronary atherosclerosis in CHD ↓ LDL-C, Total-C, Apo-B, VLDL-c, TG; ↑ HDL-C in HeFH, nFH, mixed dyslipidemia (Type IIa, IIb) ↓ TG (Type IV) Primary dysbetalipoproteinemia (Type III) [labelled for children >8]	10, 20, 40, 80 mg tablets Initial 40 mg/d od; max 80 mg/d Administer 1h before or 4h after bile acid sequestrant No ↑ risk myopathy with concurrent therapy with niacin, fibrates, CYP450 3A4 substrates§	Renal insufficiency 10 mg/d

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Drug	Trade name	Pharmacokinetics	Labelled indications* **Contraindications**† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Rosuvastatin calcium	CRESTOR®	Peak plasma concentration 3-5h; Absorption ↓ ~20% with food Primarily plasma protein-bound Bioavailability: ~20% Elimination half-life: ~19hrs Excretion: 90% in feces Unknown transfer to milk ~ 2X exposure in Asian patients compared to Caucasian Metabolized by CYP 450-2C9; no effect on CYP 450 3A4	↓ Total-c, LDL-c, ApoB, non-HDL-c, TG, and ↑ HDL-C in Primary hypercholesterolemia (HeFH and nonfamilial) and mixed dyslipidemia (Types IIa and IIb) ↓ TG (Type IV) HoFS ‡ Not studied in Type I, III and V	5, 10, 20, 40 mg tablets HeFH, nFH, mixed dyslipidemia 5-40 mg/d od; initially 5-10 and titrated as appropriate based upon monitoring 40 mg/d dose reserved for inadequate response at lower doses ↑ risk myopathy and/or rhabdomyelitis , acute renal failure with higher dose, concurrent lipid lowering therapy, cyclosporine, lopinavir/ritonavir. Use Mg or Al containing antacids 2h before or after Ros	HoFH: 20-40 mg/d Asian: 5 mg/day od initially Elderly: ≤ 5 mg/d Renal insufficiency: 5-10 mg/d (~ 3X ↑ plasma concentration) Concomitant lipid lowering therapy: ≤ 10 mg/d ↓ dose if Asian; with Cyclosporine, Warfarin

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Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Simvastatin	ZOCOR®	Plasma peak: ~ 2-4h Plasma half-life: 4-12 h Lactone hydrolyzed to β-hydroxyacid Low bio-availability in the circulation (<5%) ↑ levels with age, and renal and hepatic insufficiency Extensive first-pass extraction in the liver Highly plasma protein-bound Excretion: ~ 60% feces; ~ 13% urine No CYP450 3AC inhibition CYP450 3AC substrate	↓ risk of MI, need for revascularization, death from cardiac events, risk of stroke, TIA in HC patients with clinically evident CHD; ↓ TC, LDL-c, Apo B, non-HDL-c-c, TG; ↑ HDL-c in primary Hypercholesterolemia (HeFH and nonfamilial) Mixed dyslipidemia (Types IIa and IIb) Dysbetalipoproteinemia (Type III) Hypertriglyceridemia (Type IV hyperlipidemia) HoFH‡ Also labeled for pediatric uses	5, 10, 20, 40, 80 mg tablets 20 mg/d od in evening; titrated monthly as indicated clinically HoFH: 40 mg/d in evening or 80 mg/d in 3 divided doses ↑ myopathy with fibrates, >1g/day niacin, cyclosporin, CYP450 3A4 substrates§, HIV protease inhibitors	With concomitant lipid lowering therapy: ≤ 10 mg/d With cyclosporine or Danzol: initially 5 mg/d; ≤ 10 mg/d maximum With Amiodarone or Verapamil: ≤ 20 mg/d Renal insufficiency: 15 mg/d initially with close monitoring Contraindications: hypersensitivity, active liver disease; unexplained persistent ↑ transaminases; pregnancy; lactation

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Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Ezetimibe selective inhibitor of intestinal cholesterol and related phytosterol absorption by the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), in the brush border of the small intestine					
Ezetimibe	Zetia®	Plasma peak: 4-12 h Plasma half-life: ~ 22 hrs Highly plasma protein-bound Absorption: High inter-subject variability; unaffected by food Glucuronide conjugation ↑ levels in geriatric patients Excretion: ~ 80% feces Neither inhibitor nor inducer of CYP450 isozymes 50-80% ↓ AUC with cholestyramine bid	↓ Total-c, LDL-c, ApoB in primary hypercholesterolemia (HeFH and nonfamilial) - monotherapy and in combination with HMG-CoA inhibitors ↓ Total-c, LDL-c, ApoB, non-HDL-c-c in mixed hyperlipidemia - combination therapy with FF HoFH: in combination with Ator or Sim * ↓ sitosterol and campesterol in HoFS As appropriate upon hospitalization for an acute coronary event	10 mg tablets 10 mg od May be administered with HMG-CoA reductase inhibitor or fibrate, with awareness that monotherapy risks of other medications are magnified with co-therapy	Hepatic insufficiency: no adjustments required Renal insufficiency: no adjustments required ≥ 2 h before or ≥ 4 h after bile acid sequestrant None for race Contraindications: hypersensitivity, active liver disease; unexplained persistent ↑ transaminases; pregnancy; lactation Rhabdomyelysis and myopathy are rare on monotherapy; generally associated with concomitant use of HMG-CoA reductase inhibitor

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Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Ezetimibe/ Simvastatin	Vytorin™	Same as individual drugs above 55% ↓ AUC with bile acid sequestrant	↓ Total-c, LDL-c, ApoB, non-HDL-c, TG, and ↑ HDL-C in primary HC or mixed hyperlipidemia. (HeFH and nonfamilial) ↓ Total-c, LDL-c in primary or mixed hypercholesterolemia HoFH *	10/10, 10/20, 10/40, 10/80 mg ezitimibe/mg Sim od evening, with or without food Primary HC initially 10/10 or 10/20, titrated monthly as clinically appropriate HoFH: 10/40 - 10/80 mg/d 10/10 max with gemfibrate; caution with other fibrates, ≥1 g/d niacin With bile sequestrants, dose ≥2 h before or ≥4 h after sequestrant risk of myopathy and/or rhabdomyelitis ↑ with dose, CYP450 3A4 substrates§ 55% ↓ AUC with cholestryamine – not recommended Monitor with concomitant digoxin, warfarin	Hepatic insufficiency: not recommended Renal insufficiency: use only if Sim ≥5 mg is tolerated. ≤10/10 mg/d with cyclosporine or Danazol only if Sim ≥5 mg tolerated ≤ 10/20 mg/d with Amiodarone or Verapamil Other concomitant lipid lowering therapy: avoid - lack of safety and effectiveness data. If used, dose ≤ 10/10 mg/d Contraindications: hypersensitivity, active liver disease; unexplained persistent ↑ transaminases; pregnancy; lactation

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Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Fibrates					
Fenofibrate	TRICOR®	Insoluble in water, but readily absorbed from GI tract; ↑ absorption with food Plasma Peak fenofibric acid 6-8h Elimination t½ 20h Steady-state after 5 days dosing Highly plasma protein-bound Glucuronide conjugation Elimination: 60% of a dose in urine; 25% feces Insignificant oxidative metabolism (e.g. CYP450) Finobrate and finofibric acid do not inhibit CYP450 3A4, 2D6, 2E1, 1A2; are weak inhibitors of 2C19, 2A6; mild-to-moderate inhibitors of 2C9	↓ Total-c, LDL-c, TG, ApoB; ↑ HDL-c in primary HC (HeFH and nFH; Types IIa and IIb) - monotherapy and with statins ↓ TG in Types IV and V hyperlipidemia Contraindications: hypersensitivity; severe renal or hepatic dysfunction; unexplained persistent liver function abnormality; preexisting gallbladder disease	54, 160 mg tablets Initial dose 160 mg/d with normal renal function; reduce dose if lipid targets met Limit dose to 54 in those with moderate renal impairment, and in elderly Coumarin-type anticoagulants potentiated – monitor prothrombin times Immunosuppressants (e.g. cyclosporine) may elicit synergistic nephrotoxicity Bile acid sequestrants 1-2h after or 4-6h before fenofibrate Combine with HMG-CoA reductase inhibitors only if benefit outweighs increased risk including myopathy and/or rhabdomyelitis	

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Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Micronized fenofibrate	Lofibra®	30% ↑ absorption compared to TRICOR®, so lower once-daily dose is effective	As above	134, 200 mg tablets	
Gemfibrozil	LOPID®	Completely absorbed ↑ Cmax with dose 0.5h before meal; unchanged AUC ↓ AUC with dose after meal Highly plasma protein-bound 6% excreted in feces 70% excreted in urine; glucuronide conjugation Oxidative metabolism	↓ TG in Types IV and V hyperlipidemia at risk of pancreatitis Not indicated for Type I hyperlipoproteinemia, ↓ risk of developing CHD only in Type IIb patients with low HDL-c, high LDL-c and TG Contraindications: combination with cerivastatin (↑ risk myopathy and/or rhabdomyelitis); hepatic or severe renal dysfunction, including primary biliary cirrhosis; gallbladder disease; hypersensitivity	600 mg tablets 1200 mg/d; 600 bid, 0.5h before morning and evening meals Coumarin-type anticoagulants potentiated – monitor prothrombin times Patients taking repaglinide or gemfibrozil should not start the other; patients taking both already should carefully monitor blood glucose, and should not take itraconazole. Discontinue if lipid response not significant	Caution in pregnancy – only if potential benefit outweighs risks to fetus Unknown transfer to breast milk

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Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Niacin					
Niacin (NIR)	Niacor®	Water-soluble B-complex vitamin (note: nicotinamide not effective) Plasma peak: 30-60 min Plasma t½: 20-45 min Excretion: 88% in urine as niacin and nicotinuric acid	↓ Total-c, LDL-c in primary HC (Types IIa and IIb) ↓TG in hyperlipidemia (Types IV and V), ↑ HDL-c Not indicated in Type I hyperlipoproteinemia Contraindications: hypersensitivity; significant/unexplained hepatic dysfunction; active peptic ulcer; arterial bleeding	500 mg tablets 1-2 g, bid or tid Start with 250 mg following evening meal, increase every 4-7 days until 2 g/d. If lipid goals are not met, increase at 2-4 wk intervals to 3g/d. May increase further, generally 6g/day max. Flushing may be decreased by slowly increasing dose, pre-treatment with aspirin or other NSAID.	Use with caution: substantial alcohol consumption; history of peptic ulcer; hepatitis; hepatobiliary disease; diabetes or potential diabetes; unstable angina/MI (esp. with nitrate, calcium channel blockers or adrenergic blocking agents); increased risk R/M with HMG-CoA reductase inhibitors Pregnancy: discontinue Tx for Types IIa or IIb; assess individually for Types IV or V Nursing: transfers to milk - assess individually

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Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Niacin extended-release (NER)	NIASPAN®	Plasma half-life: NR Absorption: 60 to 76 % of dose Excretion: 60 to 76 % of dose recovered in urine; little in feces Distribution: In mice niacin and metabolites concentrate in the liver, kidney and adipose tissue. Complex metabolism	↓ Total-c, LDL-c, Apo-B and TG in primary hypercholesterolemia (HeFH and nonfamilial) and mixed dyslipidemia (Types IIa and IIb) ↓ TC in Types IV and V hyperlipidemia ↓ risk recurrent MI with history of MI and HC In combination with Lov (see below) In combination with bile acid sequestrant to slow or reverse atherosclerotic disease; ↓ Total-c, LDL-c in primary hypercholesterolemia (Type IIa) Contraindications: hypersensitivity; significant, unexplained hepatic dysfunction; active peptic ulcer; arterial bleeding	500, 750, 1000 mg Tablets swallowed whole, according to a titration schedule, at bedtime, after a low-fat snack Flushing a common side-effect - reduced with aspirin or other NSAID, avoidance of hot drinks. If awakened by flushing rise carefully, esp. if taking blood-pressure medication Retitrate after extended discontinuation Maximize time between bile acid sequestrants and niacin May be added for patients on stable dose Lov, max Lov 20 mg/d, and Niaspan 2 g/d	Caution, monitor closely: hepatic insufficiency; history of jaundice, hepatobiliary disease, peptic ulcer; renal insufficiency; diabetes/potential diabetes – monitor for dose-related ↑ glucose intolerance; unstable angina/MI (esp. with nitrate, calcium channel blockers or adrenergic blocking agents); predisposition to gout May potentiate effects of anticoagulants Monitor for hypophosphatemia Pregnancy: discontinue Tx for Types IIa or IIb; assess individually for Types IV or V

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Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Niacin extended-release / lovastatin	Advicor®	Plasma peak: Niacin 5h; Lov 2-4h Plasma half-life: Niacin 20 to 48 min; Lov 4.5 h Absorption: Niacin ~72%; systemic concentrations dose-dependent and variable; Lov Bioavailability of Niacin and Lov varies with food; tablets not interchangeable Distribution: Niacin <20% serum protein-bound, distributes into milk; Lov highly serum protein-bound Lov bioavailability ↑ with CYP450 3A4 substrates§ Excretion: >60% Niacin in urine; ~83% Lov in feces [check to make consistent with 2 ingredients above]	Not for initial therapy Primary hypercholesterolemia (HeFH and nonfamilial) and mixed dyslipidemia (types IIa and IIb) Patients treated with Lov needing lower TG or higher HDL; and Patients treated with niacin who require further LDL-lowering Contraindications – see niacin and Lov	500/20, 750/20, 1000/20 mg niacin/mg Lov Add Lov to existing niacin therapy, or titrate niacin Warning: do not substitute with equivalent dose used of crystalline niacin – possible severe hepatotoxicity Caution: alcohol consumption, history of liver disease Avoid concomitant use of fibrates unless benefit likely to outweigh potential harm (e.g. hepatotoxicity, myopathy and/or rhabdomyelitis) See also Lov, niacin	No dose adjustments reported for special populations.

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Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Bile acid sequestrants - Strong acid ion exchange resins that are not bioabsorbed, to remove bile acids from hepatic re-circulation Contraindicated with bowel obstruction or hypersensitivity to agent					
Cholestryamine	Cholestryamine	Hydrophilic In patients with partial biliary obstruction, ↓ dermal deposition lessens pruritis??	↓ LDL-c in HC Not indicated for TG only	9 g/dose (packet or scoop) mixed with liquid 1 dose od; titrated to bid after 1wk; recommended maintenance 2-4, max 6g/d as appropriate May reduce absorption of many medications and nutrients (vitamins, phosphate) – use caution when titrating dose and when discontinuing	Caution re. constipation, possible bowel obstruction; tooth discoloration, damage Caution in pregnancy/nursing due to possible nutrient deficiencies
Colestipol	Cholestid	Not applicable		5 g/scoop granules 1g tablets	
Colesevelam	Welchol	Hydrophylic, insoluble in water, not degraded by digestive enzymes Binds bile acids, including glycholic acid	Alone or with a statin to ↓ LDL-c in primary hypercholesterolemia (Type IIa)	625 mg tablets 6 tablets od or 3 bid with meals, with liquid; max 7/d No ↓ bioavailability of digoxin, Lov, metopropol, quinidine, valproic acid and warfarin Slight ↓ bioavailability verapamil	Caution re. susceptibility to vitamin K or fat-soluble vitamin deficiencies Caution re. dysphagia, swallowing disorders, severe gastrointestinal motility disorders, or major gastrointestinal tract surgery Consult physician if intending conception, pregnant or nursing

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Drug	Trade name	Pharmacokinetics	Labelled indications* Contraindications† (in addition to considerations common to the class)	Dosing	Dose adjustments for special populations
Omega-3 fatty acids					
Omega-3-acid ethyl esters	OMACOR®	Highly absorbed Mechanism poorly understood Dose-dependent ↑ serum phospholipid EPA; less marked ↑ DHA not dose-dependent Human CYP450 unknown; ↑P450 enzyme concentrations in rats	↓ very high TG (≥ 500 mg/dL) Contraindications: hypersensitivity, allergy or hypersensitivity to fish	1 g capsules (900 mg ethyl esters of omega-3 fatty acids) ~ 465 mg EPA ~ 375 mg DHA Dose: 4 g od or 2 g bid Discontinue after 2 mo if response is inadequate	Pregnancy: not studied – discontinue if pregnant or nursing Anticoagulants: monitor for increased bleeding ALT may increase in isolation - monitor

Abbreviations: ALT = Alanine transaminase, AST = aspartate transaminase, AUC = area under the curve in pharmacokinetic study, Apo A = Apo B, Cmax = maximum plasma concentration, CHD = coronary heart disease, CPK = creatine phosphokinase, d = day, DHA = docosahexaenoic acid, EPA, eicosapentaenoic acid, FH = Familial hypercholesterolemia, GI = gastrointestinal, HC = hypercholesterolemia, HoFH = Homozygous familial hypercholesterolemia, HeFH = Heterozygous familial hypercholesterolemia, HoFS = Homozygous familial sitosterolemia, LDL –c low density lipoprotein cholesterol, max = maximum, MI = myocardial infarction, mo = month, NAR = no adjustments required, nFH = Non-familial hypercholesterolemia, NR = not reported, NSAID = non-steroidal anti-inflammatory drug, od = once daily, t½ = half-life (time for concentration to decrease to half the initial level), TG = triglycerides, TIA = transient ischemic attack, Tx = treatment

Footnotes: * Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

† Hypersensitivity is a contraindication for all medications.

‡ as an adjunct to or in place of other treatments (e.g., LDL-c apheresis)

§ e.g. itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice

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Scope and Key Questions

Normal LDL-c values range from 50 to 70 mg/dL in native hunter-gatherers, newborn infants and wild primates, none of whom develop atherosclerosis.[26] Lowering of LDL-c has been shown to reduce major coronary and cerebrovascular events.[11,12,27]. Additionally, higher serum HDL-c levels have been associated with reduced CHD risk.[28,29] Early arterial atherosclerotic changes have also been shown to be positively correlated with cardiovascular events.[30,31]

Lipid modifying therapy with statins and other non-statin medications aims to reduce these major clinical events and associated mortality primarily by effecting favorable changes in LDL-c, HDL-c and TC:HDL-c ratio.

LDL-c reduction is the primary intermediate goal.[32,33] The Executive Summary of the 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 [ATP III]) considers LDL-c as primary target of lipid modifying therapy.[34].

Only one third of all patients achieve their LDL-c goals, and proportionally even fewer with established CHD do so.[35] Current statin therapy leads to moderate LDL-c reductions. Alternatives for dyslipidemic patients despite ongoing statin therapy include dose titration, combination therapy or prescribing a more efficacious statin. Increasing statin dose or potency could potentially increase frequency of important adverse events such as rhabdomyolysis and liver damage. Combining statin therapy with another lipid-modifying agent could be an alternative provided short and long-term safety and efficacy are established with evidence.[36]

The conceptual model (Figure 1) depicts the rationale behind key questions, and the specifics we explored. The model reflects the relative importance of outcomes queried in key questions and their linkages based on extant epidemiologic evidence.

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 co-administration of different lipid-modifying agents (i.e. a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

Key Question 2. Do these regimens differ in reaching LDL-targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

Key Question 3. Compared with higher-dose statins, and to one another, do combination regimens differ in benefits and harms within subgroups of patients

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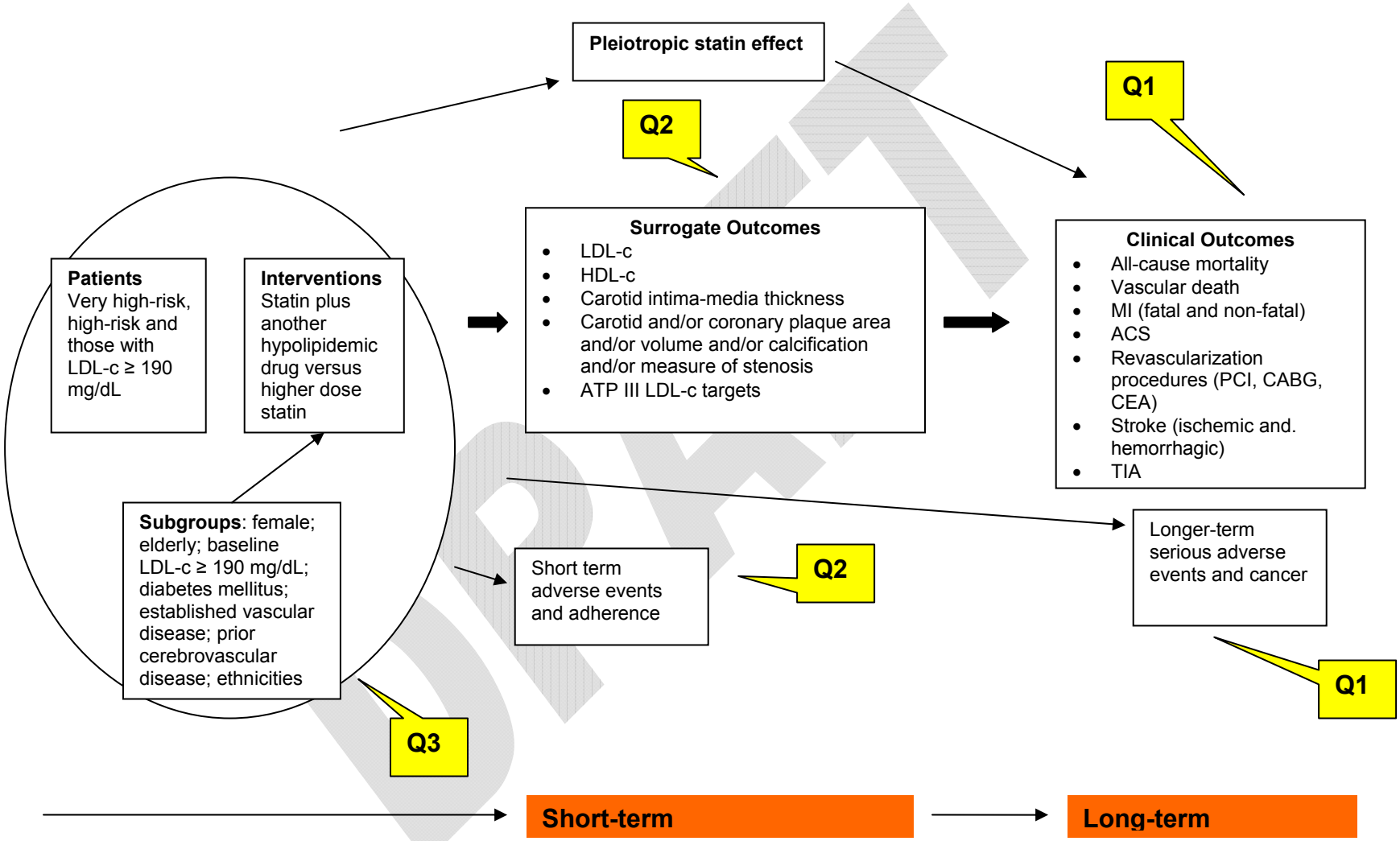
Figure 1. Conceptual Framework



Abbreviations: ACS = acute coronary syndrome ,ATPIII = Adult Treatment Panel III (of the NCEP), CABG = coronary artery bypass graft, CEA = carotid endarterectomy, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol, Q = question, TIA = transient ischemic attack

Methods

Topic Development

The topic for this report was nominated in a public process. With input from technical experts, the Scientific Resource Center (SRC) for the AHRQ Effective Health Care Program selected and refined the questions to be addressed. Initial questions were posted on a website for public feedback. Investigators at the UO-EPC, including a lipidologist and clinical specialists in relevant fields, further refined the questions with the assistance of the SRC and AHRQ.

Search Strategy

Initial and updated searches for the review were conducted in MEDLINE (1966 to July Week 4 2007), EMBASE (1980 to 2007 Week 31) and CENTRAL (The Cochrane Library, Issue 3, 2007) using the Ovid interface, and limited to English language publications from 1980 or later. Scopus was searched to identify articles cited in 8 reviewer nominated papers from earlier searches.[15,37-43] An updated and expanded search to systematically capture observational studies (i.e. without an RCT filter and without date limits) was conducted in MEDLINE (1950 to October Week 2 2007). The search strategies for each database are presented in Appendix A.

Serious or rare harms were sought by searching for named harms -- neoplasms, rhabdomyolysis, myocardial infarction, liver failure and stroke, by searching for harm related terms, and by searching for publications arising from administrative databases.[44,45] Certain harms specified in the protocol (rhabdomyolysis, stroke, myocardial infarction, cancer, liver failure and death) were sought using the relevant search terms. In order to detect unexpected serious or rare harms, harm-related terms were assembled from research on information retrieval of etiology and harms[46-48]and from previous AHRQ evidence reports.[49,50] Administrative databases included prescription claims databases, health care utilization, hospital discharge and practice-based databases and regional, and national and international surveillance systems. The search for reports from administrative databases included database names nominated by the Scientific Resource Center (personal communication, Nancy Brown SRC Research Librarian, 8/22/2006), and derived from a systematic review of biotherapeutics surveillance,[51] a previous published report of harms with statin uses,[52]as well as relevant subject headings. Main publications for certain trials were followed up through citing reference searches to attempt to identify publications that may have reported longer term followup.

Additional material from the SRC or obtained through a search of regulatory agency websites included:

- FDA-posted statistical and medical reviews of new drug applications (ezetimibe, fenofibrate, colesevalam, atorvastatin, rosuvastatin, pravastatin, lovastatin, fluvastatin, simvastatin, advicor (niacin/lovastatin), and vytorin (ezetimibe/simvastatin))
- information packages submitted by industry: Abbott (fenofibrate-statin and niacin-statin combinations); Merck (simvastatin, ezetimibe, vytorin); AstraZeneca (rosuvastatin in combination with other agents).
- grey literature reports from internet searches.

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Study Selection

Study selection was based on predefined eligibility criteria that included types of interventions, patient populations, outcome measures, and study design (Table 2). The electronic literature search, hand searched and expert-nominated records were uploaded to the software program SRS version 4.0 (Trialstat), along with forms for screening questions developed by the review team, to screen at two levels. Titles and abstracts were screened by one reviewer for potential relevance, and exclusions at this level were verified by a second reviewer. If there was disagreement or uncertainty about relevance, the record was passed through to the next level for full-text review. A priori eligibility criteria were applied to full text reports that were reviewed independently by two reviewers. Discrepancies were resolved through discussion and consensus or by third party adjudication if consensus could not be reached. Reviewers were not masked to the report's authors, institution or journal. Studies that were available only as abstracts or conference proceedings and publications that reported study design or rationale only were excluded, as were letters and editorials.

Population and health

Studies that enrolled adults (> 18 years of age) who are candidates for intensive lipid-modifying therapy were included. For the purposes of the review, an indication for intensive lipid-modifying therapy was defined on the basis of an estimated risk of > 20% for developing major cardiovascular events over 10 years, based on the Framingham global risk equations for major cardiovascular events and according to the risk categories of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).[53] Patients at high risk have either established coronary heart disease (CHD) (candidates for secondary prevention), multiple risk factors or CHD risk equivalents (candidates for primary prevention). Since individual participant risk assessments are not routinely reported, CHD risk equivalence was considered when one or more of the following criteria were met:

- report explicitly stated CHD risk equivalent status as per NCEP ATP III criteria
- participants were reported to have prior established symptomatic carotid artery disease
- participants were reported to have prior established peripheral arterial disease
- participants were reported to have prior abdominal aortic aneurysm
- participants were reported to have diabetes mellitus

Adults with isolated hypercholesterolemia and a very high LDL-c (≥ 190 mg/dL), generally associated with genetic forms of hypercholesterolemia, were also considered to be candidates for intensive lipid-modifying treatment due to the magnitude of LDL-c reduction required to reach target goals below 160 mg/dL.

Studies that enrolled patients with lower or mixed risk levels (i.e. in addition to high or very high risk) were also included since we anticipated little evidence strictly in populations of interest, and also as we aimed to explore incremental benefits of adding a non-statin drug to statin therapy with the totality of available evidence.

Data were specifically sought on the following subpopulations of interest:

- women
- elderly (≥ 80y)

- participants with baseline LDL-c above 190 mg/dL
- participants with diabetes mellitus (type 1 or 2)
- participants with established vascular disease
- participants with cerebrovascular disease
- African, Asian and Hispanic racial/ethnic groups

Interventions and comparators

The comparison of interest was statin plus another lipid-modifying therapy versus statin monotherapy (with or without a placebo). Studies that assessed the six current FDA-approved statins (atorvastatin, lovastatin, fluvastatin, simvastatin, rosuvastatin and pravastatin) were eligible.

Relevant combinations included one or more of the eligible statins mentioned above combined with one of the following in any FDA approved dose:

- niacin (short or long acting)
- peroxisome proliferator-activated receptor alpha (PPARα) agonists; i.e. fibric acid derivatives (gemfibrozil, fenofibrate, micronized fenofibrate)
- specific cholesterol absorption inhibitors (ezetimibe)
- bile acid sequestrants (colesevelam; colestipol; cholestyramine)
- omega-3 (ω-3) polyunsaturated fatty acids [e.g. eicosapentaenoic acid (EPA; 20:5 n-3), decosahexanoic acid (DHA; 22:6 n-3) and docosapentaenoic acid (DPA; 22:5 n-3)].

For omega-3 fatty acids, studies were eligible if they administered Omacor®, or dietary supplements or fish oils in which the amount and type of omega-3 fatty acid was reported.
Fixed dose combinations administered as single oral medications were included, as well as combinations administered separately. Extended release forms of medications such as fluvastatin (lescol XL), lovastatin (altocor) and niacin (niaspan) were considered as well as immediate release forms. As the number of trials comparing lower statin doses in combination with higher dose monotherapy was expected to be small, trials comparing similar doses of statins were included in the initial analyses.

The following medications, although belonging to relevant drug classes, were excluded as these have either been withdrawn from the market or are approved only outside of North America:

- cerivastatin, mevastatin, and pitavastatin
- clofibrate, cirprofibrate and bezafibrate
- colestimide

The following investigational combinations were excluded:

- statin plus one of the PPARγ agonists (thiozolidinediones)
- statin plus cholesterol ester transferase inhibitor (torcetrapib)
- statin plus plant stanols/sterols

Since pharmacodynamic pleiotropy, variable lipohilicity and drug interactions are noted for statins, [54,55] individual as well as statin class effects were investigated.

Outcomes of interest

Predefined clinical and surrogate outcomes, and outcomes of harms considered for data extraction and syntheses were:

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Clinical

- all-cause mortality
- vascular death
- fatal myocardial infarction (MI), non-fatal MI, and any or unspecified MI
- acute coronary syndrome (ACS) (encompassing unstable angina or acute MI)
- hemorrhagic stroke, ischemic stroke, any or unspecified stroke , and transient ischemic attack (TIA)
- carotid endarterectomy (CEA), percutaneous coronary interventional procedure (PCI), coronary artery bypass graft procedure (CABG), and any or unspecified revascularization procedure

Surrogate markers

- NCEP ATP III low density lipoprotein cholesterol (LDL-c) target attainment
- LDL-c
- high density lipoprotein cholesterol (HDL-c)
- total cholesterol (TC): HDL-c ratio
- measures of carotid or coronary atherosclerosis (arterial intima-media thickness, plaque area, plaque volume, arterial calcification and/or measure of stenosis)

Harms and adherence

- treatment adherence (investigator defined)
- (at least one) adverse event
- (explicitly stated) serious adverse events
- withdrawal due to adverse events
- cancer
- elevated serum AST and/or ALT above 3 times the upper limit of normal and/or hepatitis
- myalgia
- CPK above 10 times the upper limit of normal
- rhabdomyolysis (investigator defined)

We considered all-cause mortality and vascular death to be the main outcomes. We also considered the composite outcome of vascular death plus non-fatal MI plus non-fatal stroke, but based on our preliminary review of literature, this outcome was reported infrequently. Further, since only summary trial data were available, it was not possible to ascertain whether the number of patients with events was equivalent to the reported number of events because one participant might have experienced more than one non-fatal event. Thus, summing a dichotomous composite outcome from individual outcome data may introduce unit of analysis error. The composite outcome, therefore, could not be estimated for trials.

Clinical outcomes, ATP-III LDL-c target attainment, and harms outcomes were considered as dichotomous instead of count data (i.e. time-to-event data). Therefore, the proportion of participants with at least one event, and not the number of events constituted aforementioned dichotomous outcomes.

In randomized controlled trials, baseline measures are assumed to be comparable. Continuous data can, therefore, be analyzed either as post-treatment score, absolute difference (or change) from baseline or as percentage change from baseline[56] Surrogate continuous data were

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considered either as post-treatment means or mean change score from baseline, or as percentage change from baseline.

Additional intermediate markers of interest were measures of atherosclerotic plaque (carotid intima-media thickness or plaque area; coronary angiography plaque volume and degree of stenosis) and arterial calcification.

Types of studies

Because the reliability of indirect comparisons is currently poor, and the validity of the adjusted indirect comparisons depends on the internal validity and similarity of the included studies,[57] we did not consider a network meta-analysis of trials or indirect comparative syntheses based on observational studies. Further, we also considered the issue of bias and confounding ubiquitous in poorly designed observational studies. Thus, we included the following hierarchy of study design if they permitted a direct head to head comparison of combination versus statin monotherapy:

- Parallel (including factorial and crossover) randomized controlled trials
- Non-randomized studies (NRS) that were controlled clinical trials, prospective or retrospective cohort studies, nested case-control and case-control studies, and cross-sectional studies.

For efficacy/effectiveness and for short-term harm outcomes, we included head-to-head comparator randomized controlled trials (RCTs) of combination therapy versus statin monotherapy of any sample size, duration or followup, but more importance was given to longer duration, well-conducted trials that reported clinical effectiveness.

For longer-term clinical outcomes and serious adverse events, we anticipated that the available RCT data would be underpowered and decided a priori to include evidence from eligible NRS that were 24 weeks or longer in follow-up.

We did not define inclusion criteria with regards to a diet requirement or a wash-out period for previous medications prior to initiation of the study.

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Table 2. Inclusion and Exclusion criteria

Population	Adults , including healthy participants (all populations were included, not only those requiring intensive lipid lowering therapy)
Interventions	*Include* • Statin plus another hypolipidemic drug versus statin monotherapy with or without placebo (direct comparisons) • Statins - atorvastatin, simvastatin, fluvastatin, pravastatin, lovastatin or simvastatin • Nonstatin medications - ezetimibe, fibrates, niacin (IR, SR or ER), BAS or omega-3 fatty acids *Exclude* • cerivastatin, mevastatin, and pitavastatin • clofibrate, cirprofibrate and bezafibrate • colestimide • thiazolidinediones • statin plus cholesterol ester transferase inhibitor • statin plus plant stanols/sterol • any eligible drug in non-therapeutic or unapproved doses
Outcomes	• *Clinical*: all-cause mortality, vascular death, fatal myocardial infarction (MI), non-fatal MI, any or unspecified MI, acute coronary syndrome (ACS) (encompassing unstable angina or acute MI), hemorrhagic stroke, ischemic stroke, any or unspecified stroke, transient ischemic attack (TIA), carotid endarterectomy (CEA), percutaneous coronary interventional procedure (PCI), coronary artery bypass graft procedure (CABG), and any or unspecified revascularization procedure • *Surrogate*: NCEP ATP III low density lipoprotein cholesterol (LDL-c) target attainment, LDL-c, high density lipoprotein cholesterol (HDL-c), total cholesterol (TC):HDL-c ratio, and measures of carotid or coronary atherosclerosis (arterial intima-media thickness, plaque area, plaque volume, arterial calcification and/or measure of stenosis) • *Harms*: treatment adherence (investigator defined), (at least one) adverse event, serious adverse events (explicitly stated), withdrawal due to adverse events, cancer, elevated serum AST and/or ALT ≥ 3 times ULN and/or hepatitis, myalgia, CPK ≥ 10 times ULN, and rhabdomyolysis (investigator defined)
Study design	*Include - Directly comparative studies* • RCT (including factorial and crossover) of any duration; and • NRS (CCT, cohort, case-control and nested case-control, and cross-sectional) if ≥ 24 weeks and investigating clinical outcomes, SAE and cancer *Exclude* • Other observational designs • Indirect comparisons • Crossovers of less than 4 weeks washout • Crossovers without paired observations or within-person differences
Types of study	Q1: RCT and NRS (clinical case control, cohort, case-control and nested case-control, and cross-sectional) reporting clinical outcomes and/or SAE and/or cancer Q2: RCT Q3: RCT and NRS (clinical case control, cohort, case-control and nested case-control, and cross-sectional) reporting clinical outcomes and/or SAE and/or cancer
Publication	*Exclude:* full text not presented or unavailable, non-English publication, editorials

Abbreviations: ACS = acute coronary syndrome, BAS = bile acid sequestrant, CABG = coronary artery bypass graft, CEA = carotid endarterectomy, ER = extended release, HDL-c = high density lipoprotein cholesterol, IR = immediate release, , LDL-c = low density lipoprotein cholesterol, MI = myocardial infarction, NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III, NRS = nonrandomized study, PCI = percutaneous coronary intervention, RCT = randomized controlled trial, SAE = serious adverse events, SR = slow release, TC = total cholesterol, TIA = transient ischemic attack

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Data Extraction

Standardized and comprehensive online electronic data extraction forms were developed using SRS. Data extraction forms were piloted with 3 studies and identified issues were resolved. Descriptive data, outcomes, subgroup and quality assessment data were extracted, including: general study characteristics (e.g. study design and duration); population characteristics (e.g. age, gender and race/ethnicity); interventions and dosing regimens including whether conditional titration was utilized; numbers of patients randomized into relevant treatment groups; outcomes measured, method of ascertainment and the results of each outcome, including measures of variability, by relevant intervention arm. Funding source was also noted.[58]

Published data were extracted individually by members of the research team with medical and higher research degrees, and training in epidemiology and systematic review methodology (KS, AA, MA). Extracted data were checked for accuracy (inaccurate data, incomplete data, and/or irrelevant data deleted and/or corrected) and 30% of the data were randomly and independently verified another member of the research team (MS). FDA and SIP data were extracted by one reviewer (MS) and independently verified by another (FY). Minimal and occasional data accuracy checks were additionally undertaken during the process of data syntheses.

Reports belonging to the same study and participants were considered companion papers; only additional or extension phase data were extracted from companion reports. Authors were contacted for data clarification and missing data, but assumptions were not made for imputation. Furthermore, data were not imputed when they were only represented graphically. Where relevant data for multiple followup/observation periods were reported, only the longest available followup data were extracted and used.

Complex data queries were conducted using the Structured English Query Language (SEQUEL) functionality of the ACCESS program after a pilot test was refined.

With respect to crossover trials, we regarded a minimally sufficient wash-out period to be four weeks before the crossover for data extraction and synthesis eligibility. When carry-over effects were analyzed and reported, the estimate had to be non-significant. Further, crossover data were considered for extraction and syntheses only when standard deviation, standard error or confidence interval for the within-person differences were reported (or could be obtained from authors) for continuous outcomes; or dichotomous data were based on paired observations from the same individual.[59] If relevant cross-over data were not available, only pre-crossover data was extracted and synthesized. If neither, then the study was excluded because no data imputations were attempted.

For the purpose of standardizing followup from different trial reports, we considered one month to be the equivalent of four weeks, and recorded all followup periods in weeks. Only relevant trial data were extracted, synthesized and reported. For example, if a trial randomized participants to placebo, niacin, niacin and a specific statin, and statin alone, only data pertaining to the last two treatment groups would be relevant. The only exception to this was the extraction of the total number of trial participants that were randomized. Since the total number of randomized participants would be an exaggeration of the relevant population, data syntheses focused on *evaluable participants*.

The broad-cut LDL-c fraction based on beta-quantification *reference method* recommended by NCEP as the evaluating standard has been epidemiologically linked to cardiovascular

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diseases.[60-62] LDL-c (indirectly) calculated with the commonly employed Friedewald's formula agrees with β-quantification reference method up to triglyceride (TG) levels of 400 mg/dL. However, at higher TG levels (as in diabetes and non-fasting states) estimation of LDL-cholesterol by this method is not accurate.[60,61,63] The NCEP recommended that laboratories employ LDL-c assays with a total analytical error < 12%, imprecision < 4%, and inaccuracy < 4%.[63] New (third) generation of homogeneous assays directly measuring LDL-c offer the capability for fully automated measurement of LDL-c.[64] When studies reported both direct and indirectly measured LDL-c , we extracted indirectly measured LDL-c when TG < 400 mg/dL or patients were fasting. Otherwise direct LDL-c was extracted. We did not distinguish between the two modes of LDL-c measurement in quantitative or qualitative syntheses.

Biochemical data reported in SI units (e.g. LDL-c in mmol/L) were converted to mg/dL using the following conversion formula for LDL-c and HDL-c: 1 mmol/L= 38.7 mg/dL.[65]

For dichotomous outcomes, zero participants with event(s) was not assumed but had to be explicitly stated or clearly inferred. Adherence data were also extracted, if available, as a binary outcome (e.g. participants that were adherent) according to the definition provided in the respective trial reports.

Trials reported variable drug dosing regimens. We used the following guidance: *fixed* dosing was considered to occur when participants were assigned to a specific dose of drug treatment and continued throughout the trial duration. In *fixed titrated* dosing schedule, the drug dose was increased to a maximum in all participants. A *conditional titration* required only a select group not meeting pre-stated cholesterol or LDL-c criteria to be titrated to the next higher drug dose. In trials that employed fixed or conditional titration, the maximum statin dose was extracted for treatment group identification and the type of dosing regimen was noted.

Dichotomous data were extracted either as the number (n) of participants with events and the total number evaluable (N) or as summary between treatment odds with 95% Confidence interval (CI). Continuous outcomes were extracted as the mean (percentage change, change score and/or post-treatment means) with the accompanying measure of dispersion for each treatment group, or as mean difference between treatments.

When trials incorporated multiple relevant treatment arms, all were extracted as available. We noted whether extracted data belonged to a specific statin type and dose or was pooled across doses. We stipulated that only explicitly stated serious adverse events (SAE) be extracted. The United States Food and Drug Administration defines SAE as any untoward medical occurrence that at any dose, results in:[66]

- death
- is life threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly or birth defect

Quality Assessment

We used predefined criteria to evaluate the quality of included studies. Reports of RCTs were assessed using the Jadad scale, a 5 point scale that evaluates randomization, blinding, withdrawals and dropouts/ins.[67] Studies scoring 3-5 on the Jadad scale are considered to be of

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higher quality than studies scoring 0-2. Adequacy of allocation concealment was assessed as adequate, inadequate or unclear.[68]

The quality of non-randomized studies was assessed using the Downs and Black criteria.[69]. The final question of the Downs and Black instrument was operationalized to a 0 or 1 score (from a 0-5) depending whether a power or sample size calculation was reported (1) or not (0). The total Downs and Black score ranged from 0-28 with higher scores indicative of less bias.

Intention-to-treat analysis was considered to have been employed when data were reported for all randomized participants, and if that could not be ascertained, when authors reported such analysis.

Applicability

The clinically important outcomes reported, study durations, setting, participant characteristics and country of origin are reported in the results. Applicability of evidence distinguishes between *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer followup periods than most *efficacy* studies. The results of effectiveness studies are more applicable to the spectrum of patients in the community who will use combinations of lipid-modifying agents, rather than the highly selected populations in efficacy studies. We discuss applicability issues in the limitations section.

Rating the Body of Evidence

The overall strength of evidence for outcomes was assessed using a method developed by the GRADE Working Group.[70] Rating the body of evidence incorporates following key elements: study design, study quality, consistency and directness, and also considers the presence of imprecise or sparse data, probability of publication bias, evidence of a dose gradient where applicable and magnitude of the effect. Syntheses or the body of evidence are quality rated to indicate the *level of confidence* that can be placed on the summary findings:

- High = further research is very unlikely to change our confidence in the estimate of effect
- Moderate = further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate
- Low = further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate.
- Very low = any estimate of effect is very uncertain.

We used the GRADEpro software on four select important outcomes of interest for the key questions.[71] The outcomes chosen for grading the strength of evidence were:

- all-cause mortality
- vascular death
- participants experiencing serious adverse event
- participants reaching ATP III LDL-c goals

Data Synthesis

Data analyses were carried out to evaluate: 1) efficacy/effectiveness; and 2) adverse events and adherence. Each statin was considered separately for comparisons with each of the five

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possible combinations of treatment (ezetimibe, niacin, fibrates, bile acid sequestrants and omega-3 fatty acids). A total of 7440 meta-analyses were planned and data queries run (Table 3).

Non randomized studies were synthesized qualitatively, as meta-analysis of NRS is controversial.[72-74] Furthermore, estimates from individual studies are often adjusted for confounding which may vary across studies. Diversity in study designs, patient characteristics, and measurement of outcome variables in nonrandomized studies additionally appear to discourage simple quantitative summary estimation. Instead, we chose to appraise the quality of the evidence and explore their strengths and limitations.

For Key Question 1, the primary outcomes of interest were longer-term clinical outcomes and serious adverse events. Based on our preliminary review of the RCT literature, we considered *longer-term* to be a study duration period of 24 weeks or longer. Evidence from both randomized and NRS was considered. For Key Question 2, focusing on short-term intermediate measures of efficacy and harm, evidence syntheses were restricted to RCTs. For Key Question 3, both RCT and NRS evidence were considered to explore a mix of clinical and surrogate efficacy.

Dichotomous summary estimates were reported as odds ratios with 95% CIs, and continuous surrogate biochemical outcomes were pooled as mean differences in means of change scores/post-treatment means or percentage mean change from baseline.

The key questions focused on the population in need of intensive lipid lowering, and subgroups. Questions also entailed that the statin used in combination therapy be of a lower dose than monotherapy. We anticipated sparse evidence in certain populations and dose distinguishing analyses. As such we employed the following general approach in evidence syntheses while restricting the harms analyses to all available populations:

- synthesize evidence regardless of statin type and dose, and trial population (*does addition of another drug to statin therapy offer incremental benefit?*)
- synthesize evidence pertaining to lower dose of a specific statin in combination with another lipid modifying drug and higher dose of the same statin as monotherapy, regardless of trial population – atorvastatin, simvastatin and rosuvastatin were considered (*is a adding another lipid lowering drug better than increasing the statin dose?*)
- synthesize efficacy/effectiveness evidence regardless of statin type and dose, in participants requiring intensive lipid lowering and in subgroup populations
- synthesize efficacy/effectiveness evidence pertaining to a lower dose of a specific statin in combination with another lipid modifying drug, compared with higher dose monotherapy using the same statin, in participants requiring intensive lipid lowering and in subgroup population – atorvastatin, simvastatin, rosuvastatin, pravastatin, lovastatin and fluvastatin were considered

For each of these syntheses associated with clinical outcomes, serious adverse events, treatment adherence and all participants with adverse events, we conducted a sensitivity analysis on trials over 24 weeks duration where possible.

To synthesize evidence regarding those in need of intensive lipid lowering, data were considered from trials restricted to, or providing subgroup data on, those with CHD, CHD risk equivalent disease (as per NCEP ATP III criteria), and/or baseline LDL-c over 190 mg/dL. Subgroup analyses focused on participants with/of:

- baseline LDL-c ≥ 190 mg/dL
- diabetes mellitus

- established vascular disease – i.e. subgroup or full trial data on those with peripheral vascular disease, cerebrovascular disease, and/or established CAD
- cerebrovascular disease – i.e. subgroup or full trial data on those with ischemic stroke, hemorrhagic stroke, unspecified stroke and/or TIA
- African descent
- Asian descent
- Hispanic profile

Given the absence of bioequivalence studies across different statins, comparison of lower dose statin in combination therapy with higher dose statin monotherapy was statin specific. In order to avoid multiple comparisons across numerous permutations of lower versus higher dose statins, lower and higher statin doses were defined a priori as follows:

Statin	Atorvastatin	Simvastatin	Rosuvastatin	Pravastatin	Fluvastatin	Lovastatin
Lower dose (mg/day)	5 and/or 10 and/or 20	5 and/or 10 and/or 20	5 and/or 10	5 and/or 10 and/or 20 and/or 40	5 and/or 10 and/or 20 and/or 40	5 and/or 10 and/or 20 and/or 40
Higher dose (mg/day)	40 and/or 80	40 and/or 80	20 and/or 40 and/or 80	80	80	80

Trials that reported multiple treatment arms were either balanced (i.e. equal number of combination and monotherapy arms varying by statin dose only), or unbalanced. Reported data were either pooled across dose for the two categories of statin combination and monotherapy treatments, reported individually for arms, or both depending upon the comparison being explored.

Meta-analyses, or even qualitative syntheses in the face of high heterogeneity, comparing lower dose (specific) statin plus another lipid modifying drug with higher dose of the same statin as monotherapy, were not conducted when the trial:

- employed two different statin types in combination and monotherapy
- compared lower dose of a particular statin in combination with higher dose of the same statin monotherapy, but both doses met our pre-stated lower or higher dose criteria (see above). For example, atorvastatin 40mg/day in combination with another lipid lowering drug versus atorvastatin 80mg/day alone would not be considered in lower combination statin versus higher dose monotherapy syntheses, since both atorvastatin doses qualified as *higher doses*.
- reported only pooled data despite randomization of participants to appropriate lower and higher doses of statins
- employed randomization to a non-statin lipid lowering drug and placebo as add-on to background statin therapy in which participants were already taking several statins in several doses.
- employed an identical dose of statin in both combination and monotherapy arms
- employed a higher dose of statin in the combination arm(s) than monotherapy arm(s)

For meta-analyses that were not dose specific (i.e. regardless of lower and higher statin dose), pooled data for combination arms and for monotherapy arms were used when available. When pooled data were not available, and the trial had balanced multiple arms, arms using similar

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doses of statins across combination and monotherapy were used as multiple trial data but data were identified as belonging to one and the same trial by denoting it with the same author name and year of publication. For example, for a hypothetical trial published in 2008 with three combination and monotherapy arms of different statin doses:

- author 2008_1
- author 2008_2
- author 2008_3

When trials had multiple unbalanced relevant treatment arms and pooled data were not reported, then group data were pooled for each of the two categories of treatments after testing for between group (within trial) heterogeneity. Between-treatment-group heterogeneity was tested with Fisher's Exact test or Chi-square test for dichotomous outcomes, and generic inverse variance function for continuous outcomes. When between-group (within trial) heterogeneity was not high, continuous data were pooled using generic inverse variance, and binary data were pooled summing the numerators and the denominators of corresponding proportions. Pooled data were then used in the meta-analysis.

For meta-analyses that investigated lower dose statin in combination therapy compared with higher dose monotherapy using the same statin, a similar methodology for pooling within trials with multiple treatment arms was used. However, when pooling was not conducted due to statistical heterogeneity, and arms were unbalanced, specific comparisons were selected according to standard operating procedures that sought to minimize between trial heterogeneity and remove reviewers' data selection bias. Again, comparisons were entered in the meta-analysis software as if they came from different trials but identified by the one and the same author name and year of publication using the approach mentioned above. A pooling log was maintained for multiple-arm trials reporting details of within trial pooling of data, and, in the absence of pooling, log of specific treatment arms that were used.

When the same first author published two different trials in the same year, trial data were differentiated as follows:

- author year_a
- author year_b

Reported measures of dispersion varied across studies (e.g. standard deviation, standard error and confidence interval); these data were standardized for the meta-analyses. Also, if results did not include an endpoint measurement for each outcome for each patient, and the authors reported a range of evaluable participants in the data table, the lower bound of the range was used.

For surrogate outcomes, some studies may report adjusted means (least square mean), usually from an ANCOVA model. The covariates adjusted for may include gender, doses and study centre. However, the included variables differed across studies and, additionally, some studies do not identify the covariates. It was therefore not possible to combine only studies using the same analytic model.

Data from crossover trials were combined with parallel non-crossover trials only if the appropriate paired data were available.

Heterogeneity across trials was tested using an I^2 statistic,[75] and an I^2 value greater than 50% was considered substantial and pooling was not undertaken.

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All meta-analyses were based on the random effects model of DerSimonian and Laird.[76] The Comprehensive Meta-Analysis software version 2.2046 was used for all meta-analyses.

Sensitivity analyses were restricted to adequacy of allocation concealment for the main outcomes of all-cause mortality and vascular death.[77] Additionally, important analyses were those which were restricted to trials of 6-months or longer duration for clinical outcomes and serious adverse events, consistent with the specification of long term outcomes in the key questions. Dose specific met-analyses (i.e. lower dose of a specific statin in combination with another lipid lowering drug compared with higher dose monotherapy using the same statin) were considered both regardless of mode of dosing (fixed dose, fixed titrated, or conditionally titrated dosing) and those restricted to trials employing fixed dose or fixed titrated dosing regimens.

Dichotomous data with zero values (e.g. no participant experiencing myalgia) were not part of the meta-analyses because summary estimates were not estimable, but such trials, with their evaluable sample, were reported for the particular synthesis.

Publication bias was explored through funnel plots for each comparison of interest for which meta-analyses were conducted. Although other explanations exist, an asymmetric funnel plot suggests the possibility of publication bias. In addition, the degree of funnel plot asymmetry was measured by the intercept from regression of standard normal deviates against precision – the Egger's regression test.[77]

We planned to:

- present *Forest plots* for important outcomes regardless of heterogeneity as long as there were at least two trials contributing to the synthesis – namely, all-cause mortality, vascular death, participants attaining ATP-III LDL-c targets, LDL-c and serious adverse events
- conduct meta-analysis and report pooled estimate only when I^2 was not greater than 50%
- present *Funnel plots* as long as there were at least 6 included studies in an analysis
- perform *Egger's regression test* if there were more than 10 included studies in an analysis

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Table 3. A priori planned analyses regarding all participants (A), and special populations (S) requiring intensive lipid lowering therapy or of specific ethnic descent

Outcome	Sensitivity analysis	Data	Any statin	Ator	Sim	Ros	Prava	Fluv	Lov
				Lower dose statin in combination versus higher dose monotherapy • Fixed dose or fixed titration • All dosing schedules, including conditional titration					
All-cause mortality		n/N	A S	A S	A S	A S	S	S	S
All-cause mortality	*AAC*	n/N	A S	A S	A S	A S	S	S	S
Vascular death		n/N	A S	A S	A S	A S	S	S	S
Vascular death	*AAC*	n/N	A S	A S	A S	A S	S	S	S
Fatal myocardial infarction		n/N	A	A	A	A			
Nonfatal myocardial infarction		n/N	A	A	A	A			
Any myocardial infarction (STEMI and/or non-STEMI)		n/N	A	A	A	A			
Any cerebrovascular event		n/N	A	A	A	A			
Hemorrhagic stroke		n/N	A	A	A	A			
Ischemic stroke		n/N	A	A	A	A			
TIA		n/N	A	A	A	A			
Any stroke		n/N	A	A	A	A			
Acute coronary syndrome		n/N	A	A	A	A			
Carotid endarterectomy		n/N	A	A	A	A			
Percutaneous coronary intervention		n/N	A	A	A	A			
CABG		n/N	A	A	A	A			
Any revascularisation procedure		n/N	A	A	A	A			
For all clinical outcomes, consider additional analyses on trials of follow-up duration of 6 months or more where applicable									
Treatment Adherence		n/N	A	A	A	A			
All participants with adverse events		n/N	A	A	A	A			

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Outcome	Sensitivity analysis	Data	Any statin	Ator	Sim	Ros	Prava	Fluv	Lov
Serious adverse events		n/N	A	A	A	A			
Withdrawal due to adverse events		n/N	A	A	A	A			
Cancer		n/N	A	A	A	A			
Elevated AST and/or ALT > 3 times ULN and/or hepatitis		n/N	A	A	A	A			
Myalgia		n/N	A	A	A	A			
CPK > 10 times ULN		n/N	A	A	A	A			
Rhabdomyolysis (investigator defined)		n/N	A	A	A	A			
For serious adverse events, treatment adherence and all participants with adverse events, consider additional analyses on trials with follow-up duration of 6 months or more									
Participants attaining ATP III LDL-c targets		n/N	A S	A S	A S	A S	S	S	S
LDL-c									
		Post tx change in means	A S	A S	A S	A S	S	S	S
		Mean % change from baseline	A S	A S	A S	A S	S	S	S
HDL-c									
		Post tx change in means	A S	A S	A S	A S	S	S	S
		Mean % change from baseline	A S	A S	A S	A S	S	S	S
TC:HDL ratio									
		Post tx change in means	A S	A S	A S	A S	S	S	S

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Outcome	Sensitivity analysis	Data	Any statin	Ator	Sim	Ros	Prava	Fluv	Lov
		Mean % change from baseline	A S	A S	A S	A S	S	S	S
Carotid artery									
		IMT (mm)	A	A	A	A			
		plaque area	A	A	A	A			
		plaque volume	A	A	A	A			
		% stenosis	A	A	A	A			
		calcif'n	A	A	A	A			
Coronary artery									
		IMT (mm)	A	A	A	A			
		plaque area	A	A	A	A			
		plaque volume	A	A	A	A			
		% stenosis	A	A	A	A			
		calcif'n	A	A	A	A			

Analyses:
Any statin = Any statin (including mixed) + nonstatin drug, versus any statin (including mixed)
Ator = Atorvastatin 5-20 mg/day + nonstatin drug, versus Atorvastatin 40-80 mg/day
Sim = Simvastatin 5-20 mg/day + nonstatin drug, versus Simvastatin 40-80 mg/day
Ros = Rosuvastatin 5-10 mg/day + nonstatin drug, versus Rosuvastatin 20-40 mg/day
Lov = Lovastatin 5-40 mg/day + another hypolipidemic, versus Lovastatin 80 mg/day
Fluv = Fluvastatin 5-40 mg/day + ezetimibe 10 mg/day, versus Fluvastatin 80 mg/day
Prava = Pravastatin 5-40 mg/day + another hypolipidemic drug, versus Pravastatin 80
Abbreviations: calcif'n = calcification, IMT = intima-medial thickness, S = subgroup analyses (participants requiring intensive lipid lowering therapy and ethnic subgroups), Tx = treatment, X = analyses of all participants,

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Results

Search Results

Searches identified 7649 bibliographic records from searches of MEDLINE (1966 to July Week 4 2007), EMBASE (1980 to 2007 Week 31) and CENTRAL (The Cochrane Library, Issue 3, 2007) using the Ovid interface, and limited to English language publications from 1980 or later. Scopus was searched to identify articles cited in 8 reviewer nominated papers from earlier searches.[15,37-43] An updated and expanded search to systematically capture observational studies (i.e. without an RCT filter and without date limits) was conducted in MEDLINE (1950 to October Week 2 2007). The search strategies for each database are presented in Appendix A. As well, 8 records were identified by hand searching reference lists of review papers, FDA data, and information provided by drug manufacturers to the Scientific Resource Center updated as of April 2008. One report was nominated by a reviewer.

Of the 7644 unique records identified, 6977 were excluded following initial screening, and 525 studies were excluded upon full-text screening, as detailed in Figure 2.

Overall, 121 reports of 90 trials were considered for quantitative or qualitative evidence syntheses to answer questions regarding comparisons of all statin plus non-statin hypolipidemic drug combinations of interest (Tables 4,5). Of these reports, 118 were randomized and 3 non-randomized controlled trials.[78-80] Companion reports of trials occasionally contributed longer-term or additional data, but only the main trial report was used for data and trial identification (Table 6). Thirty-one reports of randomized trials were identified as companion reports, so in total 87 unique trials contributed evidence.

No studies of observational design met inclusion criteria. Eight of ten randomized controlled crossover trials were excluded because reported data did not incorporate within-person differences for continuous outcomes and paired observations for dichotomous endpoints, while pre-crossover data were not reported.[81-88] Excluded trials and reasons for exclusion are contained in Appendix B.

Eligible FDA reports were either companions of already published randomized trials contributing previously unpublished data,[89-94] or unpublished trials (Table 5).[95,96]

There were no eligible studies exclusively in women or elderly of 80 years of age or more. Four trials restricted recruitment to male gender.[97-100]

Thirty-eight authors were contacted to request additional data associated with 44 randomized controlled trials.[33,38-41,82,98,101-137] Additional data were obtained for six of forty four studies.[98,119,121,122,125,129]

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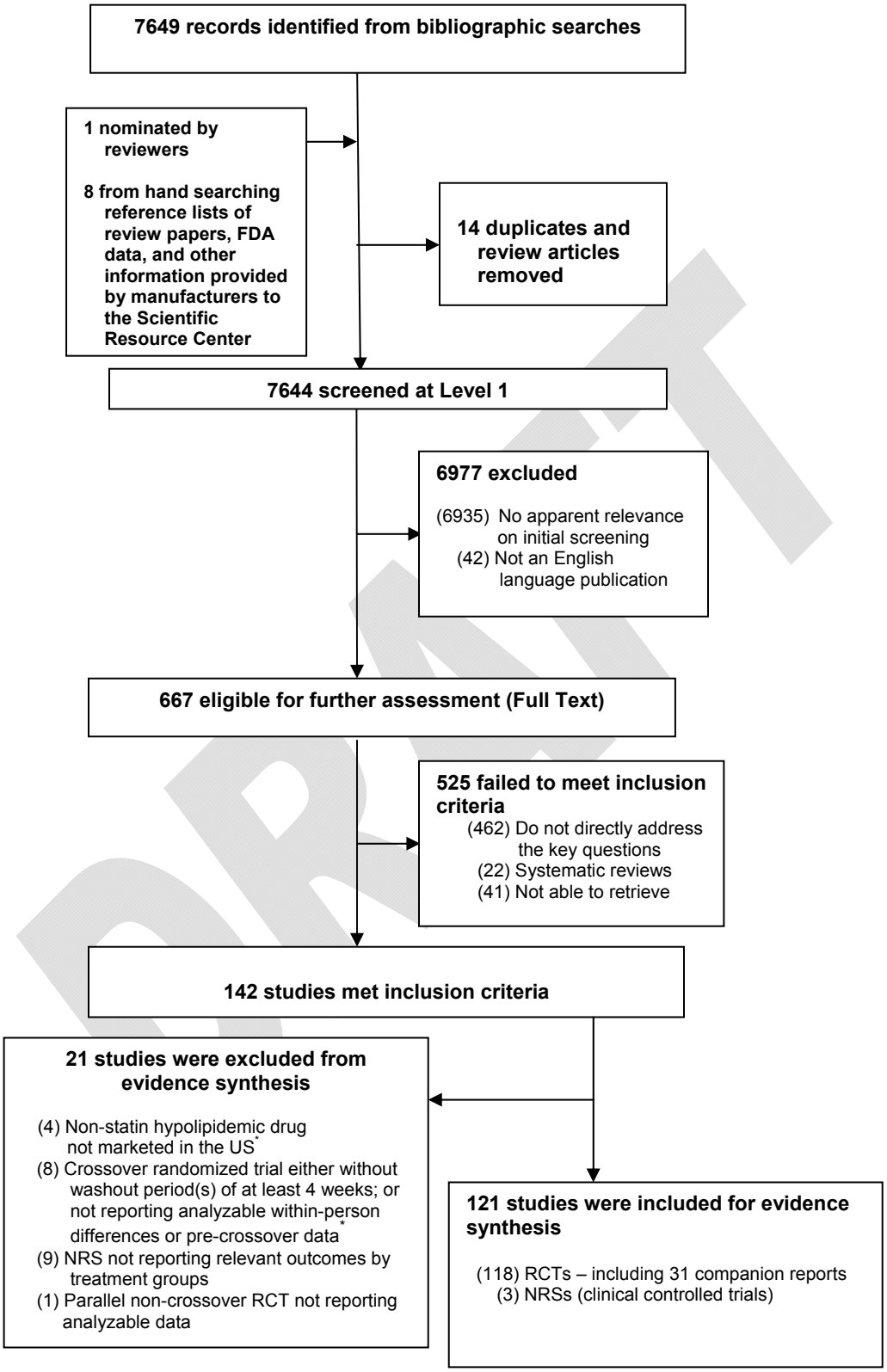
Figure 2. QUOROM Flow Chart



* One study report is common to both of these categories
Abbreviations: NRS = non randomized studies, RCT – randomized controlled trial

Table 4. Randomized controlled trials included in evidence syntheses

Trials are referenced according to the primary study
Reports in ***bold italics*** provided analyzable crossover data

Drug	Ezetimibe	Fibrates	Niacin	Bile Acid Sequestrants	Omega-3 Fatty Acids
Rosuvastatin	Kosoglou (2004)[119] Ballantyne (2007)[125]	Durrington (2004)[121]	Capuzzi (2003)[138] McKenney (2007)[122]	Ballantyne (2004)[139]	**X**
Atorvastatin	Cruz-Fernandez (2005)[110] Stein (2004)[140] Ballantyne (2003)[130] Blagden (2007)[123] Piorkowski (2007)[141]	Athyros (2005)[142] Athyros (2002)[143]	**X**	Hunninghake (2001)[101] Isaacsohn (1997)[144] Heinonen (1996)[145]	Nordoy (2001)[146] Chan (2002)[98]
Simvastatin	Rodney (2006)[128] Landray (2006)[147] Farnier (2005)[109] Brohet (2005)[111] Masana (2005)[148] Gaudiani (2005)[116] Bays (2004)[149] Feldman (2004)[38] Goldberg (2004)[39] Davidson (2002)[135] Kosoglou (2002)[97] Patel (2006)[126] Berthold (2006)[100] Chenot (2007)[131] Shankar (2007)[150] Kastelein (2008)[33]	Grundy (2005)[115] Muhlestein (2006)[129]	Stein (1996)[151]	Knapp (2001)[152] Simons (1992)[153] O'Brien (1990)[154] Johansson (1995)[117]	Hong (2004)[155] Durrington (2001)[156] Nordoy (1998)[157] Davidson (1997)[158] Liu (2003)[159] Davidson (2007)[160]

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Drug	Ezetimibe	Fibrates	Niacin	Bile Acid Sequestrants	Omega-3 Fatty Acids
Lovastatin	Kosoglou (2004)[161] Kerzner (2003)[134]	**X**	Insull, Jr. (2004)[162] Hunninghake (2003)[133] Gardner (1996)[163] FDA Report (2008)[95] FDA Report (2008)[96] ***Vacek (1995)[164]***	Davidson (2001)[165] Schrott (1995)[166]	**X**
Pravastatin	Melani (2003)[132]	Wiklund (1993)[105] Napoli (1997)[167]	O'Keefe, Jr. (1995)[168]	Eriksson (1998)[169] Ito (1997)[99] Pravastatin Multicenter Study Group II (1993)[170] Ismail (1990)[106] Barbi (1992)[108]	**X**
Fluvastatin	Stein (2008)[104]	Derosa (2004)[118] Smit (1995)[171]	**X**	Sprecher (1994)[43]	**X**
Mixed statins*	Barrios (2005)[102] Pearson (2005)[112] Ballantyne (2005)[113] Ballantyne (2004)[37] Gagne (2002)[137] ***Geiss (2005)[114]*** McKenney (2007)[122] Goldberg (2006)[127] Catapano (2006)[172] Constance (2007)[173]	Athyros (2002)[41] Shah (2007)[174]	Taylor (2004)[175] Bays (2003)[40] McKenney (2007)[122] Kuvin (2006)[176]	Simons (1998)[177]	Yokoyama (2007)[124] Meyer (2007)[178]
Total trials	13	11	37	17	10

* Either participants were on several different statins *a priori* and were randomized to add-on non-statin treatment or placebo/no drug; or statins in combination and monotherapy within a trial were not identical in type.

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Table 5. Non-randomized studies included in evidence syntheses

	Ezetimibe	Fibrates	Niacin	Bile Acid Sequestrants	Omega-3 fatty acids
Simvastatin		van Dam 2001 [78]		Mol (1990) [80]	
Lovastatin	**X**		**X**	Ojala (1990) [79]	**X**
Fluvastatin					

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Table 6. Companion reports for primary studies included in evidence syntheses

Reports in ***bold italics*** provided analyzable crossover data

Main report	Companion reports			SIP/FDA reports
Geiss (2005)[114]	***Geiss (2006)[179]***			
Pearson (2005)[112]	Pearson (2005)[180]	Pearson (2006)[181]	Denke (2006)[182]	
Capuzzi (2003)[138]	Capuzzi (2004)[183]			
Masana (2005)[148]	Gagne (2002)[136]	Simons (2004)[184]		
Davidson (2002)[135]	Sager (2003)[185]			FDA Extension Trial Report[89]
Nordoy (2001)[146]	Nordoy (2003)[186]			
Chan (2002)[98]	Chan (2002)[187]	Chan (2002)[188]	Chan (2006)[189]	
Nordoy (1998)[157]	Nordoy (2000)[190]			
Simons (1998)[177]	Simons (1998)[191]			
Wiklund (1993)[105]	Vanhanen (1995)[192]	Wiklund (1996)[193]		
Insull, (Jr. (2004)[162]	Insull (2005)[194]			
Bays (2003)[40]	Bays (2003)[195]	Bays (2003)[196]	Bays (2005)[197]	
Taylor (2004)[175]	Taylor (2007)[198]			
Athyros (2005)[142]	Athyros (2006)[199]			
Ballantyne (2005)[113]	Pearson (2007)[200]			
Ballantyne (2003)[130]	Ballantyne (2004)[201]			
Bays (2004)[149]	Ose (2007)[103]			
Goldberg (2004)[39]				FDA Extension Trial Report[90]
Knapp (2001)[152]				FDA Companion Report[91]
Gagne (2002)[137]				FDA Companion Report[92]
Melani (2003)[132]				FDA Companion Report[93]
Kerzner (2003)[134]				FDA Companion Report[94]

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Data Synthesis and Pooling

To avoid double counting a trial treatment group while quantitatively synthesizing evidence from RCTs with multiple unbalanced arms, within-trial between-treatments data pooling was undertaken after testing for statistical heterogeneity. A log of pooled trial treatment arm data, and arms that were selected for data syntheses when pooling could not be undertaken because of high or significant statistical heterogeneity, is presented in Appendix C.

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Ezetimibe Combination Therapy versus Statin Monotherapy

Overview of included studies

A total of 37 randomized controlled trials evaluated relative efficacy and/or harms of the combination of a statin plus ezetimibe (10 mg/day) compared with statin monotherapy, in a total of 20651 participants (Table 4). None of the included non-randomized studies addressed this particular comparison. Eleven randomized trials had more than one associated journal published or FDA report (Table 6). Six trials had one or more companion reports of the same trial,[112-114,132,134,137] while extension companion reports of longer treatment and followup period were associated with 5 trials.[39,130,135,148,149] The longest available data were analyzed, and one of the companion reports was considered for trial referencing.

Thirty trials were conducted in multiple centers and 6 in a single centre,[97,100,119,131,141,161] while the number of participating center(s) was not reported in one trial.[114]

Partial or complete pharmaceutical industry sponsorship was reported for 30 of 37 trials,[33,37-39,97,100,102,104,109-113,116,119,122,123,126-128,130,132,134,135,137,140,147-150,161,172,173] while funding was not reported or unclear for 4 trials.[114,125,131,141]

Total Jadad score for trials ranged from 1 to 5. Sixteen trials reported an appropriate method of randomization,[33,39,102,104,109-112,123,127,128,132,135,149,172,173] while six reported an appropriate method of double blinding.[104,109-111,128,149] Allocation concealment was reported to be adequate in 13 trials.[33,39,104,112,113,127,128,132,135,147,149,172,173]

Distribution of trials by geographical region was as follows:

- North America - 24 trials [33,37-39,97,104,110,112,113,116,122,125,127,130,132,134,135,137,140,148,149,161,172,173]
- Europe - 20 trials [33,39,100,102,104,109-111,119,123,125,126,130,131,137,140,141,147,148,173]
- Asia - 4 trials [39,102,150,173]
- Australia - 2 trials [39,173]
- Africa - 4 trials [33,125,137,140]
- Central and South America - 4 trials [39,137,140,173]
- Middle East – 2 trials [109,173]
- Not reported - two trials [114,128]

No trials reported power to assess clinical outcomes, or endpoint adjudication. Also, except for 4 trials,[88,125,127,131] active clinical adverse event data collection was either not reported or unclear. Sparse evidence in subgroups was found that directly answered Key Question 3, as summarized in Table 7.

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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 co-administration of different lipid-modifying agents (i.e. a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

Study design and population characteristics

Clinical outcomes, serious adverse events or cancer were reported for a total of 25 trials, none of crossover design, randomizing 17369 participants compared statin plus ezetimibe combination therapy with statin monotherapy.[33,38,39,102,109-112,116,123,125-128,130,132,134,135,140,147-150,172,173] No trial was exclusively in females, in participants of 80 years of age or more, or in participants of Asian or Hispanic descent. However, one trial was in those of African descent.[128] A number of trials reported the ethnic composition of the trial population:

- Nineteen trials reported a mean of 86% participants of European descent (range 54%-99%)
- Fourteen trials reported a mean of 13% of African descent (range <1%-100%)
- Five trials reported a mean of 2% of Asian descent (range <1%-4%)
- Nine trials reported a mean of 8% Hispanics (range 2%-26%)

Trial duration ranged from 6 to 96 weeks, with an average of 17 weeks. No trial excluded the female gender and on average 46% of participants were women (range 28%-76%). The average of mean ages of participants was 59 years (range of mean age, 46-66 years). Eleven trials recruited outpatients,[33,38,39,112,130,132,134,135,140,148,173] while fourteen trials did not report recruitment setting. Mean Jadad score was 3 (range, 1-5) and 11 trials had adequate allocation concealment.[33,39,112,127,128,132,135,147,149,172,173]

Trial duration ranged from 6-96 wks with an average of 17 wks. Although no trial totally excluded female gender, on average 46% of participants were women (range 28%-76%). The average of mean ages of participants was 59 years (range of mean age, 46-66 years). Eleven trials recruited outpatients,[33,38,39,112,130,132,134,135,140,148,173] while fourteen trials did not report recruitment setting. Mean Jadad score was 3 (range, 1-5) and 11 trials had adequate allocation concealment.[33,39,112,127,128,132,135,147,149,172,173]

Of these 25 trials, 12 were exclusively in participants requiring intensive lipid lowering treatment (i.e. participants with established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL).[33,38,102,109-111,116,123,125-127,173] These 12 trials randomized 5979 participants.

Across trials, participants were of diverse clinical characteristics, including those with familial hypercholesterolemia and LDL-c above 190 mg/dL,[33] diabetes mellitus,[116,127,173] established vascular disease and/or CHD risk equivalent, [38,102,109-111,123,125,126] and impaired renal function,[147]ethnicity of African descent,[128] and no prior statin exposure.[123] Nineteen trials incorporated a placebo/statin lead-in period in addition to diet, with or without a prior lipid lowering drug washout period.[33,38,39,102,109-111,116,127,128,130,132,134,135,140,147,148,172,173] Most trials excluded participants with TG over 300-600 mg/dL, recent or unstable vascular disease, uncontrolled diabetes mellitus or hypertension, liver or muscle disease, high ALT, AST and

CPK, or impaired renal function. Nine trials excluded participants with baseline LDL-c over 250 mg/dL,[39,125,128,130,132,134,135,149,172] one trial excluded those with LDL-c over 160 mg/dL despite maximal statin dose,[148] and another excluded CHD or risk equivalent participants with LDL-c over 160 mg/dL.[102] Five trials provided ezetimibe-statin combination as a combined pill,[102,127,149,172,173] 11 provided a placebo in addition to statin monotherapy,[33,109-112,123,126,128,140,147,148] and one trial used a placebo only in the extension phase of the study.[130]

Outcomes with no available Evidence

Data were not available for the following planned outcomes: any MI, non-fatal MI, cerebrovascular events, ischemic stroke, hemorrhagic stroke, transient ischemic attack, acute coronary syndrome, carotid endarterectomy, percutaneous coronary intervention, coronary artery bypass graft, or any revascularization procedure.

Longer term efficacy and serious adverse events

All-cause mortality: ezetimibe-statin combination therapy versus statin monotherapy

Key Points

- No trial comparing statin-ezetimibe combination therapy with a higher dose of statin reported estimable mortality in a population requiring intensive lipid lowering therapy
- Six trials compared statin-ezetimibe combination with statin monotherapy therapy without specifically employing higher statin monotherapy dose, and the pooled result showed no difference between these treatments for mortality

All-cause mortality was reported for 17 trials in 12273 evaluable participants (Table 8). Four trials, in 1428 evaluable participants, provided treatment and followup during 24 weeks or longer.[39,116,130,147] Of the four trials, one provided estimable mortality odds of 7.51 (95% CI 0.38, 147.37) based on 3 deaths.[147] This trial randomized 300 evaluable participants with impaired renal function and no definitive indication for cholesterol lowering, to simvastatin 20 mg/day and ezetimibe or simvastatin 20 mg/day alone, with adequate allocation concealment. Across all 17 trials assessing all-cause mortality, six trials on 3156 evaluable participants with a total of nine deaths could be meta-analyzed (Figure 3). These trials, of 6 to 52 weeks duration, did not exhibit lateral asymmetry in the funnel plot (Figure 3). Eleven trials did not observe any mortality event. There was no significant difference in odds of all-cause mortality between statin plus ezetimibe therapy and statin monotherapy in this quantitative synthesis which included studies with all statin doses and participants at any risk strata (OR 0.94; 95% CI 0.27, 3.30). Meta-analysis restricted to eight trials in 9393 evaluable participants [39,112,127,128,132,147,172,173] with adequate allocation concealment, three of which contributed evaluable data to meta-analysis,[127,147,173] resulted in a pooled odds ratio for all-cause mortality of 1.22 (0.21, 7.22) in favor of monotherapy when statin plus ezetimibe therapy was compared with monotherapy (Table 8).

One trial of 24 weeks duration, employing a fixed dose assignment, permitted a comparison of a lower dose of a statin (simvastatin 20 mg/day) plus ezetimibe with a higher dose of the same statin (simvastatin 40 mg/day). However, the odds ratio was not estimable because there were no deaths (Table 8).[116]

Nine trials with 4108 evaluable participants permitted analysis of all-cause mortality for statin-ezetimibe combination therapy versus statin monotherapy in participants requiring

intensive lipid lowering therapy.[109-111,116,123,125-127,173] Across these trials, participants were those with CHD and/or CHD risk equivalent including DM, but no trial was exclusively on participants with baseline LDL-c ≥ 190 mg/dL. Only one trial was of 24 weeks or more in duration. However, as noted above, the odds ratio was not estimable because there were no deaths.[116] Meta-analysis of five of the nine trials with estimable odds resulted in a pooled odds ratio of 0.60 (0.15, 2.39), based on a total of six deaths (Figure 4). The remaining trials did not register any death. A sensitivity analysis on the two trials with adequate allocation concealment and estimable data yielded an all-cause mortality odds ratio of 0.49 (0.06, 4.02).[127,173]

No trial with estimable mortality data yielded a comparison of lower dose statin plus ezetimibe with a higher dose of the same statin monotherapy in those requiring intensive lipid lowering.

Vascular death: ezetimibe-statin combination therapy versus statin monotherapy

Key Points

- No trials addressed the issue of lower dose combination therapy versus higher dose monotherapy in participants requiring intensive lipid lowering
- The pooled result of two trials reporting vascular mortality (irrespective of patient risk strata and statin dose) was neutral for this outcome.

Four vascular deaths were reported in two trials with 1196 evaluable participants (Table 8).[33,135] Both trials used simvastatin for combination and monotherapy, and had adequate allocation concealment. Follow-up duration was 96 weeks in one trial that registered three vascular deaths in 720 individuals, yielding an odds ratio of 2.04 (0.18, 22.59).[33] For the two trials, the pooled odds ratio of vascular death was 2.28 (0.33, 15.68) (Figure 5).

One trial of 12-week duration, with 242 evaluable participants employing fixed dose treatment, permitted a comparison of a lower dose of a particular statin (simvastatin 20 mg/day) plus ezetimibe with a higher dose of the same statin as monotherapy (simvastatin 80 mg/day). Based on a single vascular death, the odds ratio was 3.31 (0.13, 82.96).[135]

One of the two trials exclusively included participants requiring intensive lipid lowering.[33] Based on 3 vascular deaths, the odds ratio was 2.04 (0.18, 22.59) in this 96-week trial on 720 individuals with familial hypercholesterolemia and baseline LDL-c > 210 mg/dL.

There was no evidence for the comparative analysis of a specific lower dose statin in combination with ezetimibe versus higher dose of the same statin monotherapy in participants requiring intensive lipid lowering therapy.

Fatal myocardial infarction: ezetimibe-statin combination therapy versus statin monotherapy

Based on a total of 1036 evaluable participants, two trials of less than 24 weeks duration reported two participants developing fatal myocardial infarction (Table 8) .[125,140] One trial recruited participants with elevated lipid levels despite low dose atorvastatin,[140] while the other exclusively included those with CHD or risk equivalent.[125] Pooled odds were 1.00 (95% CI 0.10, 9.69). One participant died of myocardial infarction while on the ezetimibe plus statin combination (Appendix D).

Stroke: ezetimibe-statin combination therapy versus statin monotherapy

In a single trial on 200 evaluable participants with impaired renal function of 24 weeks duration, one participant developed stroke on simvastatin 20 mg/day plus ezetimibe as a combined pill.[147] Compared with simvastatin 20 mg/day plus placebo, the odds ratio was 3.15 (95% CI 0.13, 78.35).

Serious adverse events: ezetimibe-statin combination therapy versus statin monotherapy

Key points

- No consistent difference was noted between statin-ezetimibe combination and monotherapy therapy in the occurrence of SAE

Participants experiencing serious adverse events were reported for 20 trials in 11358 evaluable participants (Table 8). Six trials, including 1893 evaluable participants of whom 191 had serious adverse events, were of 24 weeks or more in duration.[39,116,130,135,147,148] However, odds ratios could not be pooled because of high statistical heterogeneity (I^2 = 56%) (Figure 6). In these longer-term trials, no consistent trend in serious adverse events was observed. Gaudiani et al.'s trial was exclusively in participants with diabetes mellitus,[116] while Landray et al focused on those with moderate to severe renal impairment.[147] Others recruited more clinically diverse participants. All six trials compared identical statins in combination and monotherapy, and all but one investigated simvastatin.[130] Two trials employed the highest label doses of statins in combination and monotherapy.[130,148] Total Jadad score varied, ranging from 2-4. Three trials adequately concealed allocation, [39,135,147] and one utilized intention-to-treat analysis.[147] Four recruited in an outpatient setting,[39,130,135,148] while the remaining two did not report this information.

Regardless of statin type, dose and trial duration, pooling of 19 of 20 trials produced an odds ratio of 1.07 (0.82, 1.39) -- one trial reported no that participant developed a serious adverse event (Figure 7). [150] There was no significant lateral asymmetry on the funnel plot, with an Egger's regression intercept of 0.58, p-value > 0.05.

Meta-analysis of two trials in 827 participants (41 with serious adverse events) comparing a lower dose of a particular statin in combination with a higher dose of the same statin produced a nonsignificant odds ratio of 1.86 (95% CI 0.60, 5.74).[38,116] Both trials of 24 and 23 weeks duration, respectively, were on participants with CHD or the risk equivalent (i.e. those requiring intensive lipid lowering) and employed lower doses of simvastatin in combination with ezetimibe versus a higher dose (40 mg/day) monotherapy. Excluding one trial that used a conditional upward titration of simvastatin,[38]the odds ratio for Gaudiani et al's trial using fixed statin dose assignments was 5.51 (95% CI 0.63, 47.94).[116]

Cancer: ezetimibe-statin combination therapy versus statin monotherapy

Eleven of a total of 971 participants developed a malignancy while on similar doses of simvastatin in combination and as monotherapy, during two trials of 24 and 48 weeks duration.[39,147] Pooling yielded a nonsignificant odds ratio of 3.99 (0.71, 22.28), (Table 8). Most trials did not report active surveillance for cancer detection nor how malignancies were defined or detected.

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Key Question 2: Do these regimens differ in reaching LDL-targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

Study design and population characteristics

Thirty seven trials, one of crossover design,[114] randomized 20651 participants to compare statin plus ezetimibe combination with statin monotherapy, and recorded one or more surrogate efficacy or harms outcomes other than serious adverse events or cancer (Table 4). There was no trial exclusively in females, while two trials exclusively recruited healthy male participants.[97,100] One trial restricted recruitment to participants of African descent [128] and three restricted recruitment exclusively to those of European descent.[97,100,161]

A number of trials reported the ethnic composition of the trial population:

- Twenty eight trials reported a mean of 88% participants of European descent (range 54%-100%)
- Sixteen reported a mean of 12% participants of African descent (range <1%-100%)
- Six reported a mean of 2% participants of Asian descent (range <1%-4%)
- Eleven trials reported a mean of 7% Hispanic poulation (range 2%-26%).

Trial duration ranged from 1-96 weeks with an average of 14 weeks. Across all trials, 43% of participants were women (range, 0-76%). The average of mean ages of participants was 56 years (range, 32-66 years). Eleven trials recruited outpatients,[33,37-39,112,122,130,132,134,135,140,148,161,173] while 21 did not report recruitment setting.[97,100,102,104,109-111,113,114,116,123,125-128,137,141,147,149,150,172] The mean Jadad score was 3 (range, 1-5) and 13 trials had adequate allocation concealment.[33,39,104,112,113,127,128,132,135,147,149,172,173]

Sixteen trials, randomizing 6165 participants, were exclusively in participants requiring intensive lipid lowering treatment (i.e. participants with established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL).[33,38,102,109-111,114,116,123,125-127,131,137,141,173]

Across trials, participants were of diverse clinical characteristics including exclusive severe hypercholesterolemia (etiology unspecified),[114] homozygous familial hypercholesterolemia [137] and familial hypercholesterolemia excluding homozygotes,[33] DM [116,127,173], established vascular disease and/or CHD risk equivalent [38,102,109-111,114,123,125,126,131,141], impaired renal function,[147]no prior statin exposure,[123] and ethnicity of African descent.[128] Four trials were exclusively on otherwise healthy hypercholestrolemic participants.[97,100,119,161] Twenty-one trials incorporated a placebo/statin lead-in period in addition to diet, with or without a prior lipid lowering drug washout period.[33,37-39,102,109-111,113,116,127,128,130,134,135,137,140,147,148,172,173] Most trials excluded participants with TG over 300-600 mg/dL, patients with recent or unstable vascular disease, uncontrolled diabetes mellitus and hypertension, liver and muscle disease or high ALT, AST and CPK, or impaired renal function. Nine trials excluded participants with baseline LDL-c over 250 mg/dL,[39,125,128,130,132,134,135,149,172] one trial excluded those with LDL-c over 160 mg/dL despite maximal statin dose,[148] and another excluded high-risk patients with LDL-c over 160 mg/dL.[102] Five trials used an ezetimibe-statin combination pill,[102,113,127,149,172,173] 17 used a placebo added to

statin monotherapy,[33,37,97,104,109-112,114,119,123,126,128,140,147,148,161] and one trial used placebo only in the extension phase of the study [130].

Surrogate efficacy measures

Participants reaching ATP III LDL-c goals: ezetimibe-statin combination therapy versus statin monotherapy

Key Points

- While only 2 trials could be pooled, most trials comparing combinations with monotherapy favored combination therapy
- Combination therapy of ezetimibe and lower dose simvastatin versus higher dose simvastatin significantly increased the probability of reaching the LDL-c target.

During 21 trials on 15193 evaluable participants, 10857 participants attained ATP III LDL-c targets (Table 9). The duration of trials ranged from six to 24 weeks. High statistical heterogeneity (I^2 = 93%) across trials precluded meta-analysis. However, in 95% of trials, odds significantly favored the statin plus ezetimibe combination. Egger's test of lateral asymmetry was not significant for the 21 trials (Figure 8). One trial comparing combination simvastatin/ezetimibe with atorvastatin monotherapy in participants with type 2 diabetes mellitus, hemoglobin A1c < 8.5% and LDL-c above 100 mg/dL,[127] demonstrated non-significant odds ratios, respectively.[127]

Restricting the analysis to participants requiring intensive lipid lowering therapy, 14 trials randomizing 6200 participants also demonstrated significant statistical heterogeneity (I^2 = 90%), precluding pooling of odds ratios.[38,102,104,109-112,116,123,125,127,148,150,173] Ninety three percent of 14 trials yielded significant odds ratios favoring concomitant statin plus ezetimibe (Figure 9). No significant asymmetry was detected in the funnel effect distribution plot. As noted in the above mentioned explanation of heterogeneity, the one outlier trial was that of Goldberg et al.[127]

Two trials, employing fixed dose and conditional statin titration, permitted comparison of a lower dose of a particular statin plus ezetimibe with a higher dose of the same drug as monotherapy. Both trials were in CHD or risk equivalent participants (i.e. those requiring intensive lipid lowering therapy).[38,116] Pooling of the two trials employing simvastatin (20mg/day) plus ezetimibe (10 mg/day) compared with simvastatin (40 mg/day) as monotherapy, yielded an overall odds ratio of 3.55 (2.18, 5.79) in favor of combination treatment (Figure 10). The odds ratio was 4.79 (95% CI 2.18, 5.79) in Gaudiani et al's fixed dose trial.[116]

LDL-c, post-treatment means or mean change scores: ezetimibe-statin combination therapy versus statin monotherapy

Key Point

- A single small trial compared lower dose statin plus ezetimibe with higher dose of monotherapy. LDL-c reduction did not differ significantly between treatment groups

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LDL-c data in the form of post-treatment means or mean change of scores was reported for thirteen trials including 2426 evaluable participants, of 1-96 weeks duration. Due to high statistical heterogeneity (I^2 = 91%) data were not pooled (Figure 11, Table 10).[33,97,100,111,119,122,125,131,137,141,147,150,161] Except for one trial in a South Asian population, all trials showed statistically significant differences in means ranging from -5 mg/dL to -72 mg/dL in favor of the statin-ezetimibe combination. Egger's regression test was not significant for the 13 trials (Figure 11).

Each of the six trials on those requiring intensive lipid lowering, with 1732 evaluable participants and followup duration ranging from 6 to 96 weeks, demonstrated significant differences in mean LDL-c reductions favoring combination therapy. Point estimates ranged from 13.5 to 72.0 mg/dL.[33,111,125,131,137] The trial by Piorkowski et al, in 51 evaluable participants with CHD previously on low dose atorvastatin of 4 weeks duration, demonstrated a non-significant reduction in favour of combination.[141] Across trials, participants were clinically diverse and included those with homozygous hypercholesterolemia,[137] familial hypercholesterolemia,[33] and those with established CAD or risk equivalent disease.[111,125,131,141] Trials also varied in terms of specific statin and dose. High statistical heterogeneity (I^2 = 86%) precluded meta-analysis. Lateral asymmetry was not evident on the funnel plot (Figure 12).

One 4-week trial permitted comparison of a lower dose statin plus ezetimibe, with higher dose monotherapy using the same drug.[141] In participants with established CHD, fixed dose treatment with atorvastatin 10 mg/day plus ezetimibe resulted in a non-significant LDL-c mean difference between treatments of -13.54 (-35.19, 8.11), favoring combination treatment in comparison with atorvastatin 40 mg/day over a 4-week period.

LDL-c, percentage mean change from baseline: ezetimibe-statin combination therapy versus statin monotherapy

Key points

- A single trial in population requiring intensive lipid lowering (diabetic patients) demonstrated a significantly greater percentage mean change for combination therapy (simvastatin + ezetimibe) compared with higher dose simvastatin.
- Most trials did not compare the combination with a higher dose but the majority favored combination therapy over same dose statin therapy for this outcome.

LDL-c data in the form of percentage mean change from baseline was reported for a total of 31 trials including 17908 evaluable participants.[33,37-39,100,102,109-113,116,119,122,123,125-128,130,132,134,135,137,140,147-150,172,173] Follow-up duration ranged from 2 to 96 weeks, but the majority of trials were 6 or 12 weeks in length.

Across trials, participant characteristics were diverse and included those who were exclusively of African descent,[128] or of South Asian descent.[150] Participants' health status varied from otherwise healthy,[100,119] to severe hypercholesterolemia,[33,114,137] established CHD or risk equivalent,[38,102,109-111,114,116,123,125-127,173] or established renal disease.[147]

Meta-analysis was not possible given high statistical heterogeneity (I^2 =98%). However, 94% of trials demonstrated significant percentage reduction from baseline in favor of the statin plus ezetimibe combination ranging from 4% to 27%, compared with statin monotherapy (Figure 13).

Two trials did not reach statistical significance. One employed identical low dose of simvastatin in combination and as monotherapy in South Asians,[150] while the other compared a titrated dose of simvastatin 40 mg/day plus ezetimibe with the same dose of rosuvastatin monotherapy [122]. Asymmetry was not evident in the funnel plot and Egger's regression test (Figure 13).

In participants who might require intensive lipid lowering therapy (i.e. participants with CHD and/or risk equivalent disease and/or those with baseline LDL-c ≥ 190 mg/dL), 15 trials with 6245 evaluable participants contributed efficacy data for statin-ezetimibe in comparison with statin monotherapy, regardless of statin dose (Table 10, Figure 14).[33,38,102,109-112,116,123,125-127,137,148,173] Statistical heterogeneity (I^2 = 94%) precluded meta-analysis. Investigated statins were simvastatin, atorvastatin and rosuvastatin, in doses varying from the lowest to highest doses on the labels. Two trials had mean baseline LDL-c above 300 mg/dL,[33,137] and another two below 100 mg/dL,[116,173] while the remaining trials had mean baseline LDL-c of 100 to 200 mg/dL. One trial was based on intention-to-treat analysis,[123] and three had adequate allocation concealment.[33,127,173] Follow-up duration was 96 weeks in one trial,[33] 12 weeks in another [137] and 5 to 8 weeks in the remaining trials. Each of the trials in participants requiring intensive lipid lowering showed significant mean differences in percentage change from baseline in LDL-c in favor of combination therapy. Mean percentage reduction ranged from 7 to 27% across trials. No significant lateral asymmetry was noted when trial estimates were plotted against their standard error (Figure 14).

Gaudiani et al's trial provided data on lower dose statin plus ezetimibe in combination, to compare with higher dose monotherapy using the same statin.[116] Simvastatin 20 mg/day plus ezetimibe was compared with simvastatin 40 mg/day, in 210 participants with type 2 diabetes mellitus, on stable doses of thiazolidinedione. Some of the participants had previously completed a simvastatin trial. They had a mean baseline LDL-c above 100 mg/dL. The percentage mean difference was -20.50% (95% CI -26.60%, -14.40%).

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HDL-c, post-treatment means or mean change scores: ezetimibe-statin combination therapy versus statin monotherapy

Key Point

- Meta-analysis of 9 trials demonstrated no significant difference in HDL-c levels following treatment with either combination or monotherapy
- A single trial compared lower dose statin-ezetimibe combination with higher dose monotherapy. No significant difference in HDL was noted between the treatment arms

Meta-analysis of nine trials randomizing 1785 evaluable participants demonstrated no significant difference in HDL-c levels following treatment (95% CI -0.27 (-1.73, 1.20)) (Table 11).[33,97,100,119,125,141,147,150,161] Four of trials were exclusively in otherwise healthy participants,[97,100,119,161] two in only males,[97,100] one on South Asians,[150] one in participants with familial hypercholesterolemia and baseline LDL-c greater than 210 mg/dL,[33] and one in those with renal disease.[147] Four trials determined HDL-c within 3 weeks of trial entry.[97,100,119,161] The trial by Kastelein et al was 96 weeks in duration.[33] One trial, that compared fixed lower dose of atorvastatin (10 mg/day) in combination with ezetimibe, with atorvastatin 40 mg/day monotherapy in participants with CHD also showed no significant difference between treatments (Table 11) .

Results across trials exhibited significant funnel asymmetry most likely due to clinical diversity in this group of studies (Figure 15).

Three trials that investigated participants in need of intensive lipid lowering could be meta-analyzed, yielding a non-significant mean difference of 0.47 mg/dL (95% CI -1.05 mg/dL, 2.00 mg/dL) (Table 11).

HDL-c, percentage mean change from baseline: ezetimibe-statin combination therapy versus statin monotherapy

Key Points

- A single trial addressing a group in need of intensive lipid lowering and comparing a lower dose statin-ezetimibe combination treatment with higher dose statin monotherapy showed no significant difference
- Combination therapy produced a greater increase in the HDL-c than monotherapy in 25 pooled trials most of which included comparisons with the same statin dose in each treatment arm

HDL-c, percentage mean change from baseline was reported for 25 trials on 15515 participants (Table 11).[33,37-39,100,102,110-112,116,119,122,123,125,130,132,134,135,140,147-150,172,173] Participant characteristics were diverse across trials, including those who were otherwise healthy,[100,119] those with CHD or risk equivalent disease [38,110,111,116,123,125,173], renal disease [147] and those of mixed CHD risk South Asians [150],. Trial duration ranged from 2-96 weeks with most of 6 or 12 week followup. Meta-analysis of these 25 trials indicated significant mean percentage increase in

HDL-c over statin monotherapy, difference in means 1.69% (95% CI 1.02%, 2.37%). This pooled estimate was not associated with significant evidence of asymmetry in the funnel plot (Figure 16).

Meta-analysis of the 11 trials exclusively on 5485 participants requiring intensive lipid lowering therapy, demonstrated nonsignificant increase over baseline in percentage HDL-c with combination therapy relative to monotherapy with a statin, 1.51% (95% CI 0.70%, 2.31%) [33,38,102,110-112,116,123,125,148,173]. The pooled estimate was associated with significant evidence of lateral asymmetry (one tailed p-value for Egger's regression intercept = 0.02) (Figure 17). One trial by Gaudiani et al. compared fixed doses of simvastatin 20 mg/day in combination therapy with 40mg/day monotherapy in 210 participants with type 2 diabetes mellitus on stable thiazolidinedione doses, with a baseline LDL-c over 100 mg/dL, some of whom had previously completed a simvastatin trial. This trial provided evidence comparing lower dose of a particular statin in combination with ezetimibe against higher dose monotherapy of the same drug.[116]The percentage mean difference was -0.10 (-3.42, 3.22).

Total cholesterol:HDL-c ratio, post-treatment means or mean change scores: ezetimibe-statin combination therapy versus statin monotherapy

A single trial on 465 participants with CHD or risk equivalent, with 6 weeks followup, employing rosuvastatin 40 mg/day in combination, compared with 40mg/day of its monotherapy demonstrated a statistically significant difference in mean change from baseline -0.61 mg/dL (95% CI -0.76, -0.47) (Table 12).[125]

There was no evidence that compared a lower dose of a specific statin in combination with ezetimibe versus higher dose of the same statin as monotherapy.

Total cholesterol:HDL-c ratio, percentage mean change from baseline: ezetimibe-statin combination therapy versus statin monotherapy

Total cholesterol:HDL-c ratio, percentage mean change from baseline was reported in 15 trials, including 9728 evaluable participants (Table 12).[39,102,110,116,122,125,130,132,134,135,140,148,149,172,173] Follow-up duration ranged from 4 to 12 weeks. Trials included participants with CHD or risk equivalents,[102,110,116,125,173] or a mixed risk group. Nine trials reported recruiting outpatients,[39,122,130,132,134,135,140,148,173]while others did not report recruitment setting. Six trials employed adequate allocation concealment [39,132,135,149,172,173] and three intention-to-treat analysis.[132,134,140] High statistical heterogeneity (I^2 = 96%) precluded pooling of data. However, all trials demonstrated statistically significant additional reductions favoring combination therapy ranging from 3 to 20%. Two trials, on participants with mixed CHD risk, demonstrated between-treatment differences in mean percentage change of less than 5%(Table 12).[122,172] The funnel plot and Egger's test, however, indicated significant lateral asymmetry (Figure 18).

Studies recruiting participants requiring intensive lipid lowering could not be pooled because of high statistical heterogeneity (I^2 = 90 %).[82,102,110,116,125,173] However, across all six trials, statistically significant and consistent additional reductions in percentage change from baseline favoring combination therapy ranged from 9 to 20% (Table 12).

One trial by Gaudiani et al compared fixed doses of simvastatin 20 mg/day plus ezetimibe with simvastatin 40mg/day, in 210 participants with type 2 diabetes mellitus on stable thiazolidinedione doses, and baseline LDL-c above 100 mg/dL, some of whom had previously

completed a simvastatin trial. The percentage mean difference favored combination therapy (-13.50% (95% CI -18.22%, -8.78%)).[116]

Measure of atherosclerosis: ezetimibe-statin combination therapy versus statin monotherapy

A single placebo-controlled trial of 2 years duration in 642 evaluable participants with familial hypercholesterolemia and previously untreated LDL-c above 210 mg/dL compared change score from baseline in mean carotid intima-media thickness measured at the common carotid arteries, carotid bulbs, and internal carotid arteries.[33] Compared with simvastatin 80 mg/day as monotherapy, simvastatin 80 mg/day in combination with ezetimibe did not significantly change the arterial wall thickness. The combination therapy group experienced a mean increase of 11.1 μm, in contrast with 5.8 μm in the monotherapy group. The mean difference in change score in carotid intima-media thickness was 0.01 mm (95% CI -0.01 mm, 0.02 mm) (Table 13).

Measures of Treatment Adherence and Harms

Participants adherent to treatment: ezetimibe-statin combination therapy versus statin monotherapy

In eleven trials with a total of 5201 evaluable participants, 4608 individuals were considered to have adhered to trial medications per investigators' criteria.[33,37,39,110,122,125,126,132,135,140,147] Trial populations were clinically diverse and followup ranged from 6 to 96 weeks. Five trials did not add a placebo to statin monotherapy,[39,122,125,132,135] and no trial used a single pill for the combination treatment. The pooled odds ratio, regardless of the type or dose of statin, was 0.97 (95% CI 0.73, 1.29), and the Egger's regression intercept was not significant for lateral asymmetry (Figure 19). Restricting the meta-analysis to the three trials (total evaluable N=1711) of 24 weeks or more in duration remained nonsignificant (OR 0.95, (95% CI 0.56, 1.63).[33,37,147]

Treatment adherence for 268 evaluable participants with hypercholesterolemia was estimated from a single trial of 12 weeks duration employing lower dose statin plus ezetimibe, compared with higher dose statin monotherapy without a placebo. Treatment adherence was less likely with simvastatin 10 to 20 mg/day plus ezetimibe, compared with simvastatin 40 to 80 mg/day, with an odds ratio of 0.53 (95% CI 0.21, 1.30) (Table 14).[135]

Participants with at least one adverse event: ezetimibe-statin combination therapy versus statin monotherapy

Adverse events such as myalgia, hepatitis and elevated CPK, AST or ALT were reported for 17 trials.[37-39,102,114,119,125,127,128,130,132,134,135,140,148-150] With 4451 out of 8557 participants experiencing events, the pooled odds ratio was 0.98 (95% CI 0.89, 1.08). Trial populations were clinically diverse and followup ranged from 2 to 52 weeks. There was no evidence of significant funnel plot (Figure 20). Meta-analysis restricting to four trials of 24 weeks or more treatment duration in 2102 evaluable participants, also demonstrated non-significant odds between treatments (OR = 1.06 (0.85, 1.33)).[37,39,130,148]

One trial of 23 weeks duration allowed comparison of a lower dose of simvastatin (conditionally titrated) plus ezetimibe with a higher dose of simvastatin monotherapy, in 362 evaluable participants with CHD or risk equivalent disease. [38] The odds of an individual experiencing any adverse event with combination therapy compared with monotherapy was 1.07 (0.66, 1.73) (Table 14).

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Participants withdrawing due to adverse events: ezetimibe-statin combination therapy versus statin monotherapy

In 25 trials with a total of 11530 evaluable participants, 436 individuals withdrew due to adverse events.[33,37-39,97,102,104,110,111,116,123,125-128,130,132,134,135,137,140,148-150,173] Trial populations were clinically diverse and followup ranged from 2 to 96 weeks. One trial reported zero withdrawals.[150] The pooled odds ratio for all statin types and doses was 1.20 (95% CI 0.97, 1.48), but the Egger's regression intercept was significant for lateral funnel plot asymmetry (Figure 21).

The odds ratio for withdrawal from treatment with a lower dose of a statin plus ezetimibe compared with higher dose of the same statin monotherapy was estimated from three trials comparing fixed dose or conditional titration of simvastatin 10 to 20 mg/day with simvistatin 40 to 80 mg/day in participants with hypercholesterolemia.[38,116,135] Among 1095 evaluable participants, 52 withdrew over 12 to 24 weeks, yielding an odds ration of 1.02 (95% CI 0.49, 2.10). Restricting the meta-analysis to the two trials employing fixed statin dosing resulted in an odds ratio of 1.16 (95% CI 0.31, 4.40) (Table 14).[116,135]

Participants with AST and/or ALT above 3 times the upper limit of normal, and/or hepatitis: ezetimibe-statin combination therapy versus statin monotherapy

In 24 trials reporting this composite outcome, of a total of 14659 evaluable participants, 109 developed laboratory and/or clinical evidence of hepatic dysfunction.[37-39,97,104,110,111,113,114,116,123,125,127,128,130,132,134,135,137,140,148,149,172,173] Trial populations were clinically diverse and followup ranged from 2 to 52 weeks. Five trials did not provide estimable odds as no participant had any elements of this composite outcome.[97,111,114,123,128] Pooled odds ratio regardless of the type of statin or dose was 1.40 (95% CI 0.90, 2.19), while the Egger's regression intercept was not significant for lateral asymmetry (Figure 22).

Odds of developing one of the composite outcomes with a lower dose of a particular statin plus ezetimibe compared with the same statin monotherapy could be estimated from four trials employing fixed dose or conditional titration in 1473 evaluable participants with hypercholesterolemia, 8 of whom developed laboratory and/or clinical evidence of hepatic dysfunction.[38,39,116,135] Simvastatin 10 to 20 mg/day compared with simvastatin 40 to 80 mg/day yielded an odds ratio of 1.11 (95% CI 0.30, 4.14). Restricting the meta-analysis to the three trials employing fixed statin dosing resulted in an odds ratio of 0.98 (95% CI 0.23, 4.13) (Table 14).[39,116,135]

Participants with myalgia: ezetimibe-statin combination therapy versus statin monotherapy

Among 15 trials, 125 (2.4%) of 5050 evaluable participants reported symptoms of myalgia.[39,97,100,102,109,119,123,125,130,131,135,140,148,149,161] Trial populations were clinically diverse and followup ranged from 1 to 52 weeks. In two trials no participants developed myalgia.[100,131] The pooled odds ratio regardless of the type of statin or dose was 0.92 (95% CI 0.64, 1.33), while Egger's regression intercept was not significant for lateral asymmetry (Figure 23).

No trial provided evaluable data comparing a lower dose of a particular statin plus ezetimibe with a higher dose of the same statin monotherapy.

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Participants with CPK above 10 times the upper limit of normal: ezetimibe-statin combination therapy versus statin monotherapy

In 29 trials reporting CPK, 39 (0.2%) of a total of 19132 evaluable participants developed elevations in CPK more than 10 times upper limit of normal.[33,37-39,97,102,104,109-114,116,122,123,125,127,128,130,132,134,135,140,147-150,172] Trial populations were clinically diverse and followup ranged from 2 to 96 weeks. Fourteen trials did not provide estimable odds as no participant developed CPK elevations to this extent.[97,102,104,110-112,114,122,123,125,127,134,147,148] This included a 12 week trial in 133 evaluable participants with previously documented statin associated myopathy, treated with fluvastatin 80 mg/day in combination or monotherapy. Pooling of 15 trials yielded an odds ratio of 0.78 (95% CI 0.41, 1.49). The Egger's regression was not significant for lateral asymmetry (Figure 24).

Two trials, both in those with CHD and risk equivalent disease, permitted comparison of lower dose statin plus ezetimibe with higher dose of the same statin monotherapy.[38,116] The pooled odds ratio was 0.64 (95% CI 0.03, 13.99} for lower combination versus higher monotherapy dose simvastatin (Table 14). Of the two trials, Gaudiani et al's with fixed rather than conditional dose assignment yielded an odds ratio of 3.23 (95% CI 0.13, 80.29).[116]

Participants with rhabdomyolysis: ezetimibe-statin combination therapy versus statin monotherapy

Seventeen trials reported rhabdomyolysis, including a 12 week trial in 133 evaluable participants with previously documented statin associated myopathy, treated with Fluvastatin 80 mg/day in both combination and monotherapy.[37-39,102,104,109-111,125,128,131,134,137,140,148-150] Trial populations were clinically diverse and followup ranged from 1 to 48 weeks. Five trials employed low dose statins both as combination and monotherapy.[102,109-111,150] Rosuvastatin was investigated only in one trial.[125] Across all 17 trials and 7461 evaluable participants, no case of rhabdomyolysis was reported (Table 14).

One trial compared lower dose statin plus ezetimibe with higher dose monotherapy using the same statin. No case of rhabdomyolysis was reported in 613 participants randomized to simvastatin 10 to 20 mg/day plus ezetimibe or doses titrated up to simvastatin 40 mg/day as monotherapy.[38]

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Key Question 3: Compared with higher dose statins, and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

Study design and population characteristics

The availability of trials addressing aspects of question 3 are depicted in Table 7.

Table 7: Availability of evidence addressing ezetimibe key question 3

Condition	All-cause mortality	Vascular death	Participants reaching ATP-III LDL-c targets	LDL-c		HDL-c		TC:HDL-c ratio	
				Post-treatment or change score	*% change from baseline*	*Post-treatment or change score*	*% change from baseline*	*Post-treatment or change score*	*% change from baseline*
LDL-c ≥ 190 mg/dL	No available evidence	√	No available evidence	√	√	√	√	No available evidence	No available evidence
diabetes mellitus	√	No available evidence	√	No available evidence	√	No available evidence	√	No available evidence	√
Established vascular disease	√	No available evidence	√	√	√	√	√	No available evidence	√
Cerebro-vascular disease	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence
African descent	√	No available evidence	√	No available evidence	√	No available evidence	√	No available evidence	No available evidence
Asian descent	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence	No available evidence
Hispanic descent	No available evidence	No available evidence	√	No available evidence	√	No available evidence	√	No available evidence	No available evidence

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Longer term outcomes

All-cause mortality: ezetimibe-statin combination therapy versus statin monotherapy

Participants with diabetes mellitus . Three deaths were reported among 3 trials, in 2101 evaluable participants with diabetes mellitus. One trial of 24 weeks duration comparing fixed lower dose simvastatin plus ezetimibe with higher dose monotherapy reported no death.[116] The pooled odds ratio was 0.49 (95% CI 0.06, 4.02), with followup ranging from 6 to 8 weeks

(Figure 25).[127,173] The two pooled trials adequately concealed treatment allocation and specifically compared simvastatin combination therapy with atorvastatin monotherapy.

Odds were not estimable for a specific lower dose statin plus ezetimibe compared with higher dose monotherapy (Table 8).[116]

Participants with established vascular disease. Two vascular deaths were reported among five trials with a total of 1539 evaluable participants, all with 6 week followup.[109-111,123,126] Three trials reported zero deaths.[109,111,123] Odds of all-cause mortality were nonsignificant 0.34 (95% CI 0.04, 3.25) for combination versus monotherapy (Figure 26). Both pooled trials reported unclear allocation concealment.

There was no evidence comparing a specific lower dose combination statin versus higher dose monotherapy.

Participants of African descent. No mortality was noted over the 6 month trial by Rodney et al, using simvastatin 20 mg/day with placebo or ezetimibe in 247 individuals.[128]

There was no evidence comparing a lower dose statin in combination therapy with higher dose monotherapy using the same statin.

Vascular death: ezetimibe-statin combination therapy versus statin monotherapy

Three deaths from cardiovascular causes were reported for Kastelein et al's 2 year trial in 720 randomized participants with familial hypercholesterolemia, with baseline LDL-c over 210 mg/dL. Fixed dose simvastatin 80 mg/day was employed both in combination and monotherapy. The odds ratio of vascular death was 2.04 (95% CI 0.18, 22.59) for the combination therapy, compared with monotherapy.[33]

Surrogate outcomes

Participants reaching ATP III LDL-c goals: ezetimibe-statin combination therapy versus statin monotherapy

Participants with diabetes mellitus. Six trials in a total 3452 evaluable participants, with an average of 6 weeks followup, reported a cumulative 2370 (69%) reaching ATP III LDL-c goals.[110,112,116,127,148,173] Atorvastatin and simvastatin were employed, in varying doses. Significant statistical heterogeneity (I^2 = 92%) precluded meta-analysis. One trial included those on stable thiazolidinedione therapy,[116] one was in participants who also had established CHD, [110] and another included only those not already at their ATP III targets.[112] Three trials had adequate allocation concealment,[112,127,173] and three reported recruitment from outpatient settings.[112,148,173] Five of six trials demonstrated significant odds in favor of combination treatment ranging from 1.78 to 23.96 (Figure 27). No laterally asymmetry was evident on the funnel plot [fp].[110,112,116,148,173]

Gaudiani et al's trial in 70 evaluable participants allowed comparison of a lower dose of a statin plus ezetimibe with higher dose monotherapy using the same statin. The odds ratio of 4.79 (95% CI 1.72, 13.35) favored the lower dose simvastatin plus ezetimibe combination.

Participants with established vascular disease. Five trials, with 827 of 1538 evaluable participants achieving ATP III LDL-c goals, could not be pooled due to statistical heterogeneity (I^2 = 72%) (Figure 28).[109-111,123,150] However, all five trials showed significant odds ratios in favor of combination treatment, with odds ratio point estimates ranging from 3 to 19.

There was no evidence comparing any specific lower dose statin plus ezetimibe with higher dose monotherapy.

Participants of African descent. Pearson et al reported subgroup data on participants of African descent with established CHD on various statin therapies.[112] ATP III LDL-c goals were achieved by 109 of 208 evaluable participants of African descent with odds in favour of combination therapy (OR 3.47 (1.90, 6.33)).

There was no evidence comparing lower dose statin plus ezetimibe therapy with higher dose statin monotherapy using the same statin.

Participants of Hispanic descent. Pearson et al reported subgroup data on participants of Hispanic descent with established CHD on various statin therapies.[112] ATP III LDL-c goals were achieved by 54 of 113 participants with odds favouring combination treatment (OR = 7.82 (3.14, 19.45)).

There was no evidence comparing a specific lower dose statin plus ezetimibe with higher dose statin monotherapy.

LDL-c, post-treatment means or mean change scores: ezetimibe-statin combination therapy versus statin monotherapy

Participants with LDL-c above 190 mg/dL. Two trials randomizing 765 evaluable participants with homozygous [137] or familial hypercholesterolemia,[33] of 12 and 96 weeks duration respectively, yielded a pooled mean difference of – 51.69 mg/dL (95% CI -59.91 mg/dL, -43.48 mg/dL) (Figure 29).

There was no evidence comparing a specific lower dose statin plus ezetimibe with higher dose statin monotherapy.

Participants with established vascular disease. A total of 502 evaluable participants with established vascular disease were randomized in three trials of less than 12 weeks duration.[111,131,141] Significant differences in means favored combination treatment, with point estimates ranging from -35.00 to -13.54. However, statistical heterogeneity I^2 = 94 %) precluded meta-analysis (Figure 30).

One trial permitted comparison of statin plus ezetimibe with higher dose monotherapy with the same statin.[141] In participants with established CHD, fixed dose treatment with atorvastatin 10 mg/day plus ezetimibe was compared with atorvastatin 40 mg/day over a 4 week period. LDL-c mean difference between treatments was -13.54 mg/dL (95% CI -17.82 mg/dL, -9.26 mg/dL).

LDL-c, percentage mean change from baseline: ezetimibe-statin combination therapy versus statin monotherapy

Participants with LDL-c above 190 mg/dL. Meta-analysis of two trials with 754 evaluable participants with homozygous and non-homozygous familial hypercholesterolemia yielded a difference in percentage mean change from baseline of -16.50 (95% CI -16.63, -16.37) in favor of combination treatment (Figure 31).[33,137] Trials lasted 12 and 96 weeks respectively.

There was no evidence comparing a specific lower dose combination statin versus higher dose monotherapy of the same statin in this subgroup.

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Participants with diabetes mellitus. Each of the four trials with 1776 evaluable participants providing evidence for this subgroup analysis showed significant differences in mean percentage change from baseline favoring combination treatment, with point estimates ranging from -17.66 to -6.70 (Figure 32).[116,127,148,173] As noted previously, clinical and study design diversity was evident across trials.

Gaudiani et al's trial provided data evaluable for lower dose statin plus ezetimibe compared with higher doses of the same statin.[116] It compared fixed doses of simvastatin 20 mg/day in combination with simvastatin 40mg/day, in 210 participants with type 2 diabetes mellitus and baseline LDL-c over 100 mg/dL, on stable thiazolidinedione doses, some of whom had previously completed a simvastatin trial. The percentage mean difference favoring combination therapy was -20.50% (95% CI -26.60%, -14.40%).

Participants with established vascular disease. Across five trials with relevant data, 1348 participants with CHD demonstrated significant differences in mean percentage change from baseline favoring combination treatment with point estimates in the range of -26.90 to -14.10 [109-111,123,126]. However, trial mean differences data could not be pooled because of heterogeneity (I^2 = 90%). All trials were 6 weeks in duration, but statin types and doses varied.

There was no evidence comparing a specific lower dose combination statin with higher dose monotherapy in this subgroup.

Participants of African descent. Meta-analysis of available data from two trials with 515 evaluable participants of African descent could not be pooled because of high heterogeneity (I^2 = 72 %). However, both trials were associated with significant differences in mean percentage change from baseline favoring combination treatment, -17.20% (95% CI -21.13%, -13.27%) and -23.00% (95% CI -27.55%, -18.45) over a 12 and 6 week period, respectively (Figure 34).[112,128]

There was no evidence comparing a specific lower dose statin plus ezetimibe with higher dose monotherapy using the same statin in either subgroup.

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Participants of Hispanic descent. Over a six week followup, 147 Hispanic participants on ongoing statin therapy were randomised to add-on ezetimibe and placebo.[112] The difference in mean percentage change from baseline was -21.10 (-27.16, -15.04) in favor of combination therapy.

There was no evidence comparing a specific lower dose statin plus ezetimibe with higher dose monotherapy using the same statin in either subgroup.

HDL-c, post-treatment means or mean change scores: ezetimibe-statin combination therapy versus statin monotherapy

Participants with LDL-c above 190 mg/dL. Kastelein et al's 2 year trial in 720 randomized participants with familial hypercholesterolemia was the only available evidence demonstrating a nonsignificant difference in means of 0.20 mg/dL (95% CI -1.81 mg/dL, 2.21 mg/dL). Fixed dose simvastatin 80 mg was employed both as combination and monotherapy [33].

Participants with established vascular disease. In Piorkowski et al's trial in participants with CHD previously on low dose atorvastatin, 51 evaluable participants using lower dose atorvastatin plus ezetimibe compared with higher dose monotherapy had mean HDL-c increase nonsignificantly by 2.32 mg/dL (95% CI 0.72 mg/dL, 3.92 mg/dL) over a 4 week period.[141]

HDL-c, percentage mean change from baseline: ezetimibe-statin combination therapy versus statin monotherapy

Participants with LDL-c above 190 mg/dL. Kastelein et al's 2 year trial in 720 randomized participants with familial hypercholesterolemia yielded a nonsignificant difference in percentage mean increase of 2.40% (95% CI -0.23%, 5.03%). Fixed dose simvastatin 80 mg was employed both as combination and monotherapy.[33]

Participants with diabetes mellitus. Four trials in 2176 participants with diabetes could not be pooled, given high statistical heterogeneity (I^2 = 56.89%).[112,116,148,173] Follow-up duration ranged from 6-24 weeks and only two trials reported adequate allocation concealment.[112,173] All participants reported previous statin exposure, and one trial included those who received concomitant treatment with thiazolidinediones.[116] Pearson et al's trial presented subgroup data on participants with DM who were randomized to ezetimibe and placebo in addition to ongoing heterogeneous statin treatment.[112] Three of four trials demonstrated non-significant differences in mean HDL-c, while the largest trial by Pearson and associates in 1127 participants with DM reported an increase in mean HDL-c of 2.70% (1.25%, 4.15%) in favor of combination therapy in participants not at ATP III LDL-c targets at randomization.

Gaudiani et al's trial provided data comparing lower dose statin plus ezetimibe with higher doses of the same statin.[116] It compared fixed doses of simvastatin 20 mg/day plus ezetimibe with simvastatin 40mg/day and investigated 210 participants with type 2 diabetes mellitus on stable thiazolidinedione doses, and baseline LDL-c over 100 mg/dL, some of whom had previously completed a simvastatin trial. The percentage mean difference was -0.10% (95% CI -3.42%, 3.22%).

Participants with established vascular disease. A total of 502 evaluable participants with established vascular disease were randomized in three trials of less than 12 weeks duration.[111,131,141] Significant differences in means favored combination treatment, with point estimates of -35 and -28 were observed in two trials.[111,131] The 4 weeks trial by Piorkowski et al., in 51 evaluable participants with CHD previously on low dose atorvastatin, demonstrated a non-

significant reduction in favour of lower dose atorvastatin plus ezetimibe combination in comparison with atorvastatin 40 mg/day monotherapy. Overall statistical heterogeneity (I^2 = 94 %) precluded meta-analysis (Figure 30).

There was no evidence comparing a specific lower dose combination statin with higher dose monotherapy in this subgroup.

Participants of African and Hispanic descent. Pearson et al reported subgroup data on participants of African and Hispanic descent. Participants on ongoing statin therapy were randomised to add-on ezetimibe or placebo. The mean differences in percentage change in HDL-c in participants of African descent were 3.30% (95% CI 0.35%, 6.25%), and 0.30% (95% CI -3.64%, 4.24%) in those of Hispanic descent.[112]

There was no evidence comparing a specific lower dose combination statin versus higher dose monotherapy in both subgroups.

Total cholesterol:HDL-c ratio, percentage mean change from baseline: ezetimibe-statin combination therapy versus statin monotherapy

Participants with diabetes mellitus. Three trials with 1049 evaluable participants yielded this ratio. Statistical heterogeneity between trials precluded meta-analysis I^2 = 75%). Trials varied in population characteristics, statins and doses employed, concomitant medication, racial distribution, adequacy of allocation concealment and treatment duration.[116,148,173] The individual mean differences in percentage change from baseline significantly favored combination therapy, with point estimates in the range of -17.30 to -10.32.

Participants with established vascular disease. A single trial by Cruz-Fernandez et al randomized participants with established CHD on prior low dose atorvastatin therapy to ezetimibe or placebo. A significant mean difference in percentage change from baseline of -19.90% (95% CI -22.31%, -17.49%) was noted in favor of combination treatment.[110]

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Tables and Figures: Ezetimibe - Statin Combination Therapy versus Statin Monotherapy

Table 8. Quantitative syntheses of longer term outcomes (clinical, serious adverse events and cancer), for ezetimibe plus statin combination therapy compared with statin monotherapy

	Number of trials reporting outcome	Number in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
All-cause mortality						
All trials, ≥ 24 weeks followup [39,116,130,147]	4	1428	3 (data from single trial)	7.51	0.38	147.37
All trials [39,109-112,116,123,125-128,130,132,134,147,172,173]	17	12273	9	0.94	0.27	3.30
All trials with adequate allocation concealment [39,112,127,128,132,147,172,173]	10	9394	6	1.22	0.21	7.22
Participants requiring intensive lipid lowering therapy (DM, trial duration 24 wks) *Simvastatin* - Lower dose combination therapy versus higher dose monotherapy [116]	1	214	0	-	-	-
Participants requiring intensive lipid lowering therapy [109-111,116,123,125-127,173]	9	4108	6	0.60	0.15	2.39
Participants requiring intensive lipid lowering therapy due to diabetes mellitus - Adequate allocation concealment [127,173]	2	1887	3	0.49	0.06	4.02
Participants with diabetes mellitus [116,127,173]	3	2101	3	0.49	0.06	4.02
Participants with established vascular disease [109-111,123,126]	5	1539	2	0.34	0.04	3.25
Participants of African descent [128]	1	247	0			
Vascular death						
All trials ≥ 24 weeks followup [33]	1	720	3	2.04	0.18	22.59
All trials [33,135]	2	1196	4	2.28	0.33	15.68
All trials with adequate allocation concealment[33,135]	2	1196	4	2.28	0.33	15.68
Simvastatin - lower dose (20mg/day) combination therapy versus higher dose (80/mg/day) monotherapy [135]	1	242	1	3.31	0.13	82.96

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	Number of trials reporting outcome	Number in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Participants requiring intensive lipid lowering therapy, with LDL-c≥190 mg/dL [33]	1	720	3	2.04	0.18	22.59
Fatal Myocardial Infarction						
All trials [125,140]	2	1036	2	1.00	0.10	9.69
Participants requiring intensive lipid lowering therapy[125]	1	468	1	2.91	0.12	71.84
Stroke (ischemic and/or hemorrhagic)						
Stroke [147]	1	200	1	3.15	0.13	78.35
Serious Adverse Event(s)						
All trials, ≥ 24 weeks followup [39,116,130,135,147,148]	*6*	*1893*	*191*	-	-	-
All trials [38,39,102,109-111,116,123,125-128,130,135,140,147-150,172]	20	11358	361	1.07	0.82	1.39
Simvastatin Lower dose statin in combination therapy versus higher dose monotherapy Fixed dose only [116]	1	214	41	5.51	0.63	47.94
Simvastatin Lower dose statin in combination therapy versus higher dose monotherapy Participants requiring intensive lipid lowering Fixed and/or conditional titration[38,116]	2	827	41	1.86	0.60	5.74
Cancer						
All trials[39,147]	2	971	11	3.99	0.71	22.28

Abbreviations: CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

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Table 9. Quantitative syntheses of incidence of participants attaining ATP III LDL-c targets, for ezetimibe plus statin combination therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Relative probability of attaining ATPIII LDL-c goal						
All trials[38,102,104,109-113,116,123,125,127,130,132,134,135,140,148,150,172,173]	21	15193	10856	-	-	-
Participants requiring intensive lipid lowering therapy[38,102,104,109-112,116,123,125,127,148,150,173]	14	6200	4199	-	-	-
Simvastatin						
Lower dose statin in combination versus higher dose monotherapy	2	427	278	3.55	2.18	5.79
Participants requiring intensive lipid lowering therapy[38,116]						
Participants with diabetes mellitus[110,112,116,127,148,173]	6	3452	2370	-	-	-
Participants with established vascular disease[109-111,123,125,150]	5	1538	827	-	-	-
Participants of Hispanic descent[112]	1	113	54	7.82	3.14	19.45
Participants of African descent[112]	1	208	109	3.47	1.90	6.33

Abbreviations: ATP III = third Adult Treatment Panel of the National Cholesterol Education Program, CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

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Table 10. Quantitative syntheses of LDL-c data, for ezetimibe plus statin combination therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant treatment groups	Point Estimate	Lower CI	Upper CI
Difference in mean LDL-c post-treatment / change score from baseline (mg/dL)					
All trials[33,97,100,111,119,122,125,131,137,141,147,150,161]	13	2426	-	-	-
Participants requiring intensive lipid lowering therapy All trials[33,111,125,131,137,141]	6	1732	-	-	-
Atorvastatin Lower dose statin in combination therapy versus higher dose monotherapy Participants requiring intensive lipid lowering therapy[141]	1	51	-13.54	-35.19	8.11
Participants with LDL-c ≥ 190 [33,137]	2	765	-51.69	-59.91	-43.48
Participants with vascular disease [111,131,141]	3	502	-	-	-
Difference in mean LDL-c percentage change from baseline (%)					
All trials [33,37-39,100,102,109-113,116,119,122,123,125-127,127,128,130,132,134,135,137,137,140,147-150,172,173]	31	17908	-	-	-
Participants requiring intensive lipid lowering therapy [33,38,102,109-111,116,123,125-127,137,148,173]	15	6245	-	-	-
Simvastatin Lower dose statin in combination therapy versus higher dose monotherapy Participants requiring intensive lipid lowering therapy All participants with diabetes mellitus [116]	1	210	-20.50	-26.60	-14.40
Participants with baseline LDL-c>190 mg/dL [33,137]	2	754	-16.50	-16.63	-16.37
Participants with diabetes mellitus[116,127,148,173]	4	1776	-	-	-
Participants with vascular disease[109-111,123,126]	5	1348	-	-	-
All participants of African descent [112,128]	2	515	-	-	-
All participants of Hispanic descent [112]	1	147	-21.10	-27.16	-15.04

Abbreviations: CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

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Table 11. Quantitative syntheses of HDL-c data, for ezetimibe plus statin combination therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant treatment groups	Point estimate	Lower CI	Upper CI
Difference in mean HDL-c post-treatment/change score from baseline (mg/dL)					
All trials [33,97,100,119,125,141,147,150,161]	9	1785	-0.27	-1.73	1.20
Participants requiring intensive lipid lowering therapy [33,125,141]	3	1236	0.47	-1.05	2.00
Atorvastatin Lower dose statin in combination therapy versus higher dose monotherapy Participants requiring intensive lipid lowering therapy due to vascular disease [141]	1	51	2.32	-5.78	10.42
Participants with LDL-c>190 mg/dL [33]	1	720	0.20	-1.81	2.21
Difference in mean HDL-c percentage change from baseline (%)					
All trials [33,37-39,100,102,110-112,116,119,122,123,125,130,132,134,135,140,147-150,172,173]	25	15515	1.69	1.02	2.37
Participants requiring intensive lipid lowering therapy [33,38,102,110-112,116,123,125,148,173]	11	5485	1.51	0.70	2.31
Simvastatin Lower dose statin in combination therapy versus higher dose monotherapy Participants requiring intensive lipid lowering therapy (diabetes mellitus) [116]	1	210	-0.10	-3.42	3.22
Participants with LDL-c>190 mg/dL [33]	1	720	2.40	-0.23	5.03
Participants with diabetes mellitus [112,116,148,173]	4	2176			
Participants with vascular disease [111,123]	3	559	-0.37	-2.49	1.74
All participants of African origin [112]	1	167	3.30	0.35	6.25
All participants of Hispanic origin [112]	1	147	0.30	-3.64	4.24

Abbreviations: CI = 95% confidence interval, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol

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Table 12. Quantitative syntheses of TC:HDL-c ratio data, for ezetimibe plus statin combination therapy compared with statin monotherapy

	Number of trials	Number of participants in relevant intervention groups	Point estimate	Lower CI	Upper CI
Difference in mean TC:HDL-c ratio post-treatment/change score from baseline					
All trials [125] The trial investigated participants in need of intensive lipid lowering therapy, those with CHD or risk equivalent status	1	465	-0.61	-0.76	-0.47
Difference in mean TC:HDL-c ratio percentage change from baseline					
All trials [39,102,110,116,122,125,130,132,134,135,140,148,149,172,173]	15	9728			
Participants in need of intensive lipid lowering therapy [102,110,116,125,148,173]	6	2380			
Simvastatin Lower dose simvastatin in combination therapy versus higher dose simvastatin monotherapy	1	210	-13.50	-18.22	-8.78
Fixed dosing Participants with diabetes mellitus [116] All participants with diabetes mellitus [116,148,173]	3	1049			
Participants with vascular disease [110]	1	444	-19.90	-22.31	-17.49

Abbreviations: CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol, TC = total cholesterol

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Table 13. Quantitative synthesis of carotid intima-media thickness data, for ezetimibe plus statin combination therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant treatment groups	Point estimate	Lower CI	Upper CI
Mean difference in CIMT change score (mm)					
All trials [33]	1	680	0.01	-0.01	0.02

Abbreviations: CI = 95% confidence interval, CIMT = carotid intima-media thickness

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Table 14. Quantitative syntheses of short term harms and adherence to treatment, for ezetimibe plus statin combination therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Adherence to treatment						
All trials [33,37,39,110,122,125,126,132,135,140,147]	11	5201	4608	0.97	0.73	1.29
Simvastatin Lower dose statin in combination therapy versus higher dose monotherapy[135]	1	268	242	0.53	0.21	1.30
Participants experiencing at least one adverse event						
All trials [37-39,102,114,119,125,127,128,130,132,134,135,140,148-150]	17	8557	4451	0.98	0.89	1.08
Simvastatin Lower dose statin in combination therapy versus higher dose monotherapy Conditionally titrated dose (Fixed or conditional titration) [38]	1	362	242	1.07	0.66	1.73
Withdrawal due to an adverse event						
All trials [33,37-39,97,102,104,110,111,116,123,125-128,130,132,134,135,137,140,148-150,173]	25	11530	436	1.20	0.97	1.48
Simvastatin Lower dose statin in combination therapy versus higher dose monotherapy Fixed dose[116,135]	2	482	20	1.16	0.31	4.40
Simvastatin Lower dose statin in combination therapy versus higher dose monotherapy Fixed dose or conditionally titrated [38,116,135]	3	1095	52	1.02	0.49	2.10
AST and/or ALT ≥ 3 times the upper limit of normal, and/or hepatitis						
All trials [37-39,97,104,110,111,113,114,116,123,125,127,128,130,132,134,135,137,140,148,149,172,173]	24	14659	109	1.40	0.90	2.19
Simvastatin Lower dose statin in combination therapy versus higher dose monotherapy[39,116,135]	3	871	7	0.98	0.23	4.13

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	Number of trials reporting outcome	Number of participants in relevant intervention groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Simvastatin Lower dose statin in combination therapy versus higher dose monotherapy[38,39,116,135]	4	1437	8	1.11	0.30	4.14
Myalgia						
All trials[39,97,100,102,109,119,123,125,130,131,135,140,148,149,161]	15	5050	125	0.92	0.64	1.33
CPK ≥ 10 times the ULN						
All trials[33,37-39,97,102,104,109-114,116,122,123,125,127,128,130,132,134,135,140,147-150,172]	29	19132	39	0.78	0.41	1.49
Simvastatin Lower dose statin in combination therapy versus higher dose monotherapy[38]	1	213	1	3.23	0.13	80.29
Simvastatin Lower dose statin in combination therapy versus higher dose monotherapy[38,116]	2	815	3	0.64	0.03	13.99
Rhabdomyolysis (investigator defined)						
All trials[37-39,102,104,109-111,125,128,131,134,137,140,148-150]	17	7461	0	-	-	-
Simvastatin Lower dose statin in combination therapy versus higher dose monotherapy[38]	1	613	0	-	-	-

Abbreviations: ALT = alanine transaminase, AST = aspartate transaminase, CI = 95% confidence interval, CPK = creatine phosphokinase

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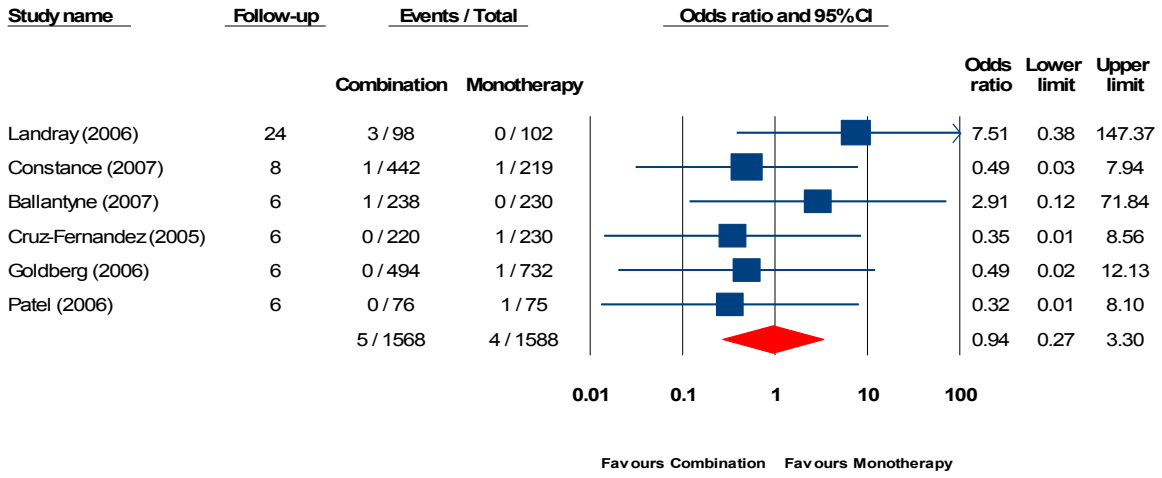
Figure 3. Forest and funnel plots of all-cause mortality for ezetimibe plus statin therapy compared with statin monotherapy in all participants



I-squared = 0.00

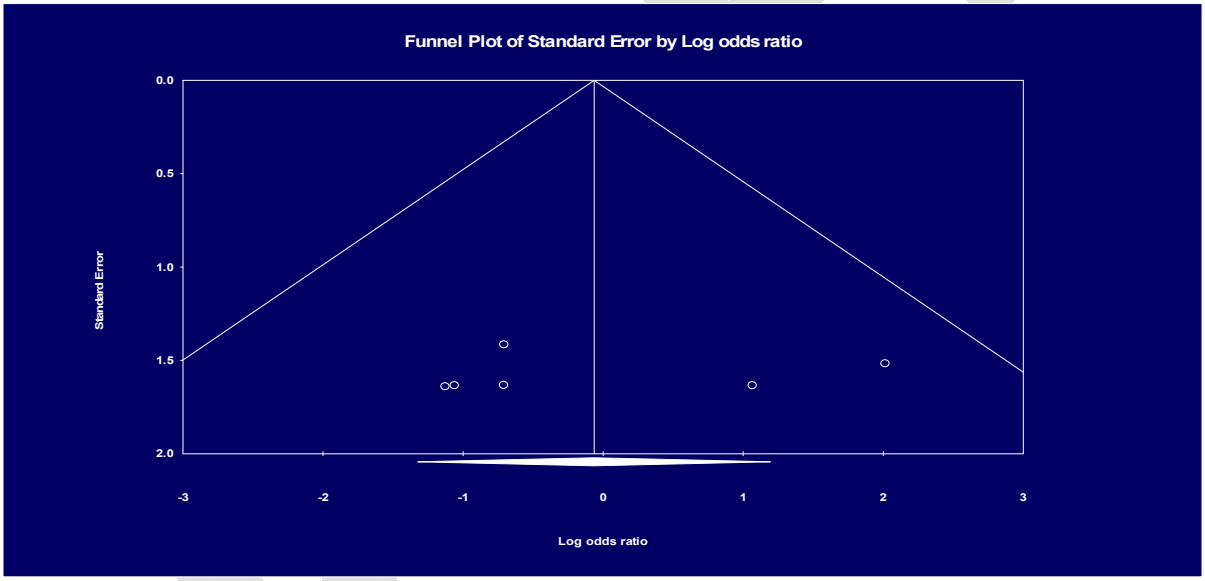


Figure 4. Forest plot of all-cause mortality for ezetimibe plus statin therapy compared with statin monotherapy in all participants requiring intensive lipid lowering therapy

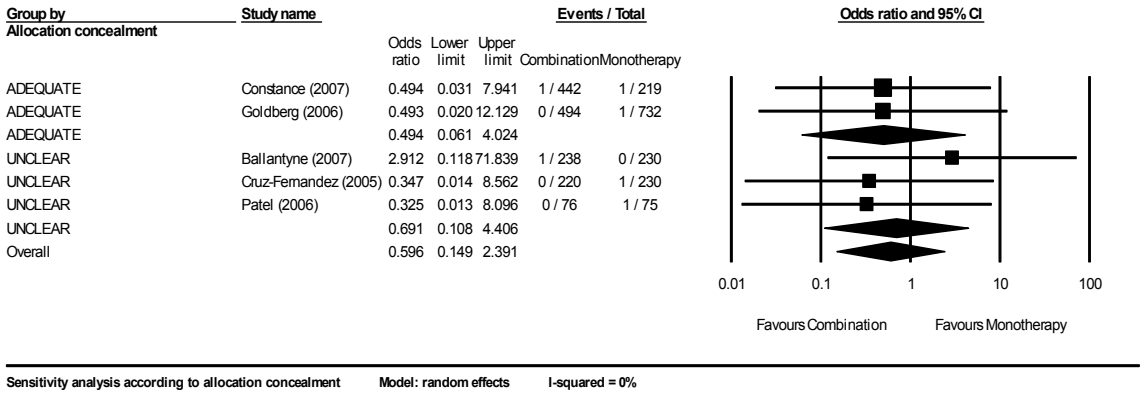


Figure 5. Forest plot of vascular death for ezetimibe plus statin therapy compared with statin monotherapy in all participants

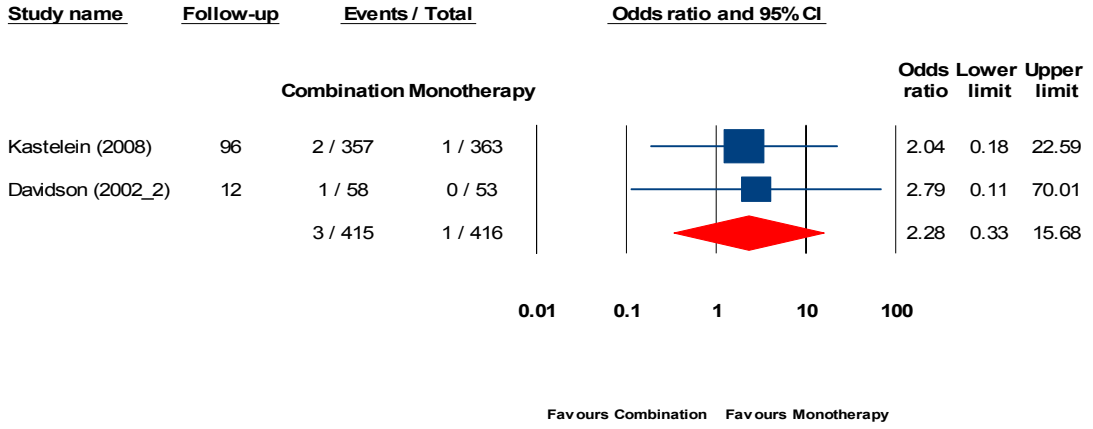
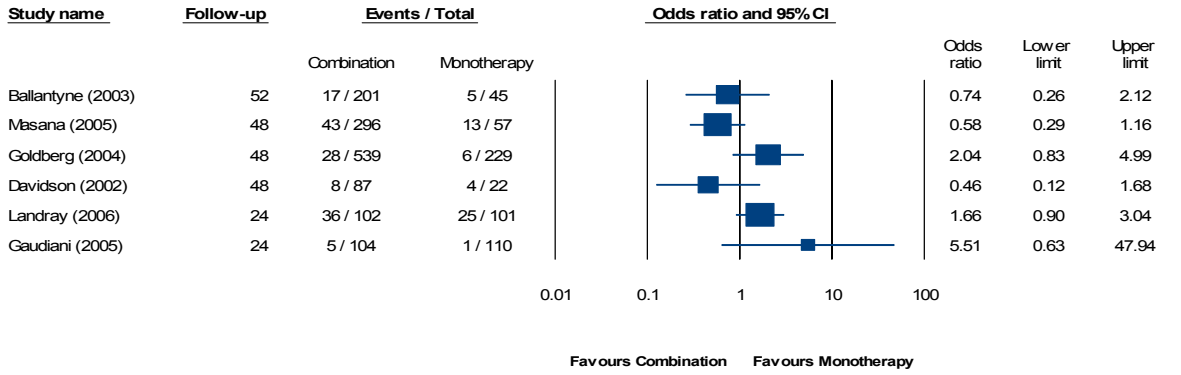


Figure 6. Forest plot of serious adverse events for ezetimibe plus statin therapy compared with statin monotherapy in trials 24 weeks or more duration



I-squared = 55.78

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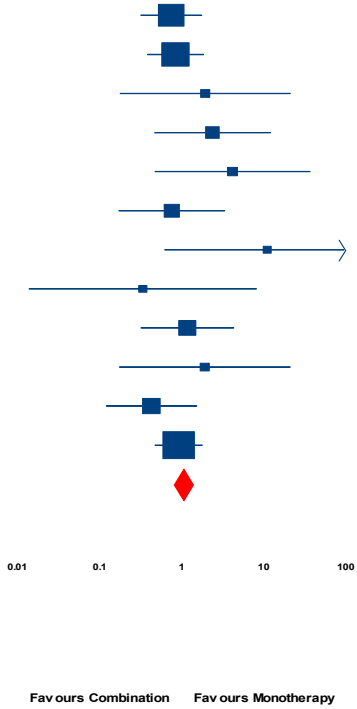
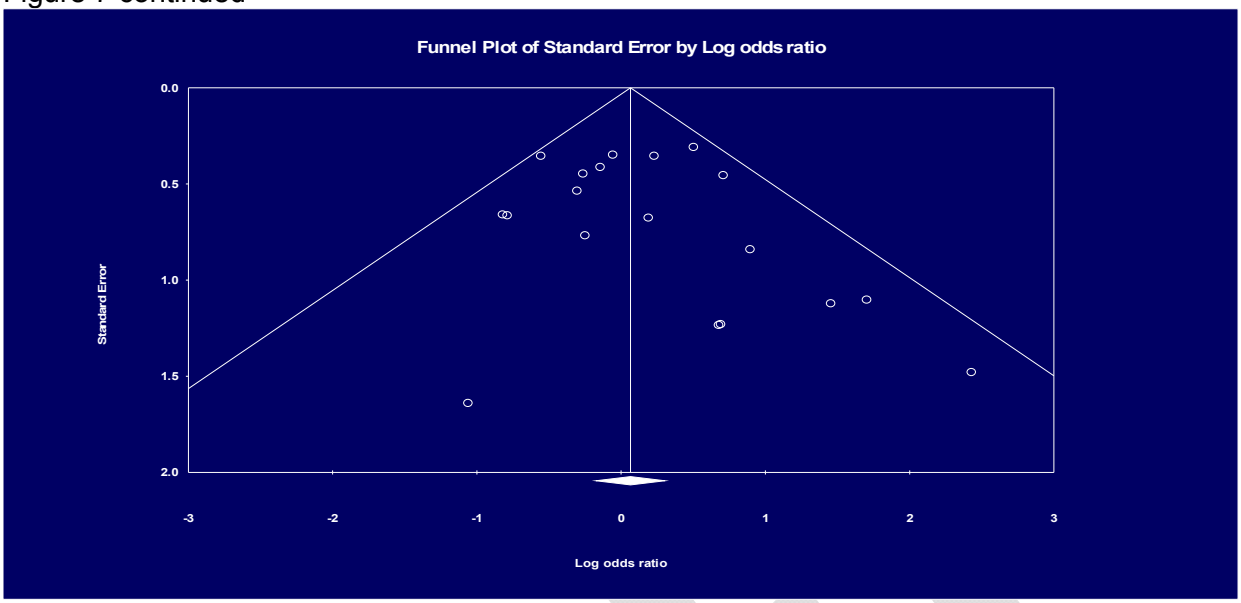
Figure 7. Forest and funnel plots with Egger's regression test, of serious adverse events for ezetimibe plus statin therapy compared with statin monotherapy in all participants

Study name	Follow-up	Events / Total		Odds ratio and 95%CI	Odds ratio	Lower limit	Upper limit
		Combination	Monotherapy				
Ballantyne (2003)	52	17 / 201	5 / 45		0.74	0.26	2.12
Masana (2005)	48	43 / 296	13 / 57		0.58	0.29	1.16
Goldberg (2004)	48	28 / 539	6 / 229		2.04	0.83	4.99
Davidson (2002)	48	8 / 87	4 / 22		0.46	0.12	1.68
Landray (2006)	24	36 / 102	25 / 101		1.66	0.90	3.04
Gaudiani (2005)	24	5 / 104	1 / 110		5.51	0.63	47.94
Feldman (2004)	23	27 / 457	12 / 253		1.26	0.63	2.53
Stein (2004)	14	9 / 305	12 / 316		0.77	0.32	1.86
Bays (2004)	14-26	11 / 544	13 / 560		0.87	0.39	1.96
Rodney (2006)	12	2 / 124	1 / 123		2.00	0.18	22.35
Barrios (2005)	6	5 / 221	2 / 214		2.45	0.47	12.79
Farnier (2005)	6	4 / 181	1 / 191		4.29	0.48	38.78
Cruz-Fernandez (2005)	6	3 / 220	4 / 230		0.78	0.17	3.53
Brohet (2005)	6	5 / 208	0 / 210		11.38	0.63	207.10
Blagden (2007)	6	0 / 72	1 / 76		0.35	0.01	8.66
Ballantyne (2007)	6	5 / 238	4 / 230		1.21	0.32	4.57
Patel (2006)	6	2 / 77	1 / 75		1.97	0.18	22.23
Goldberg (2006)	6	3 / 494	10 / 732		0.44	0.12	1.61
Catapano (2006)	6	16 / 1437	17 / 1447		0.95	0.48	1.88
		229 / 5907	132 / 5221		1.07	0.82	1.39



I-squared = 12.13

Figure 7 continued



Egger's regression intercept

Intercept	0.58764
Standard error	0.55750
95% lower limit (2-tailed)	-0.58858
95% upper limit (2-tailed)	1.76385
t-value	1.05407
df	17.00000
P-value (1-tailed)	0.15330
P-value (2-tailed)	0.30660

Figure 8. Forest and funnel plots with Egger's regression test, of participants attaining ATP III LDL-c targets for ezetimibe plus statin therapy compared with statin monotherapy in all participants

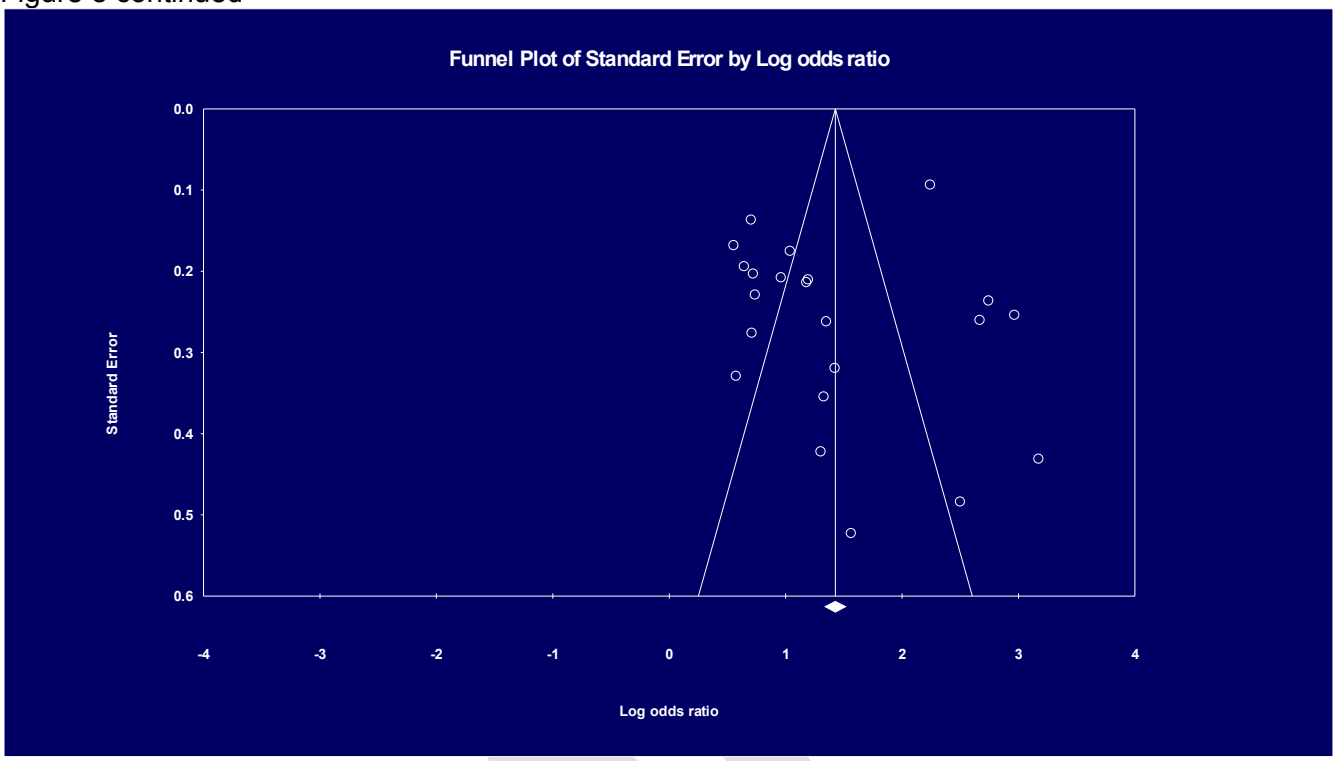
Study name	Follow-up	Events / Total		Odds ratio and 95% CI			
		Combination	Monotherapy		Odds ratio	Lower limit	Upper limit
Feldman (2004)	23	363 / 451	147 / 248		2.83	2.01	4.00
Stein (2004)	14	67 / 278	22 / 290		3.87	2.31	6.47
Ballantyne (2003)	12	215 / 252	180 / 245		2.10	1.34	3.29
Melani (2003)	12	144 / 204	97 / 203		2.62	1.74	3.94
Kerzner (2003)	12	127 / 192	107 / 220		2.06	1.38	3.08
Davidson (2002)	12	207 / 268	167 / 261		1.91	1.30	2.80
Shankar (2007)	12	101 / 114	78 / 116		3.79	1.89	7.59
Stein (2008)	12	54 / 64	41 / 69		3.69	1.61	8.44
Masana (2005)	8	61 / 73	14 / 80		23.96	10.28	55.84
Barrios (2005)	6	169 / 217	109 / 210		3.26	2.14	4.96
Farnier (2005)	6	133 / 179	31 / 186		14.46	8.67	24.10
Cruz-Fernandez (2005)	6	178 / 219	49 / 225		15.59	9.80	24.81
Brohet (2005)	6	164 / 204	36 / 207		19.48	11.83	32.06
Pearson (2005)	6	1377 / 1940	199 / 968		9.45	7.86	11.36
Ballantyne (2005)	6	828 / 923	752 / 927		2.03	1.55	2.65
Gaudiani (2005)	6-24	28 / 37	13 / 33		4.79	1.72	13.35
Blagden (2007)	6	66 / 72	36 / 76		12.22	4.73	31.58
Ballantyne (2007)	6	221 / 235	182 / 230		4.16	2.22	7.79
Goldberg (2006_1)	6	215 / 238	197 / 240		2.04	1.19	3.51
Goldberg (2006_2)	6	226 / 242	214 / 241		1.78	0.93	3.40
Catapano (2006)	6	1368 / 1427	1328 / 1428		1.75	1.25	2.43
Constance (2007)	6	392 / 442	154 / 219		3.31	2.19	5.00

0.01 0.1 1 10 100

Favours Monotherapy Favours Combination

I-squared = 93.11

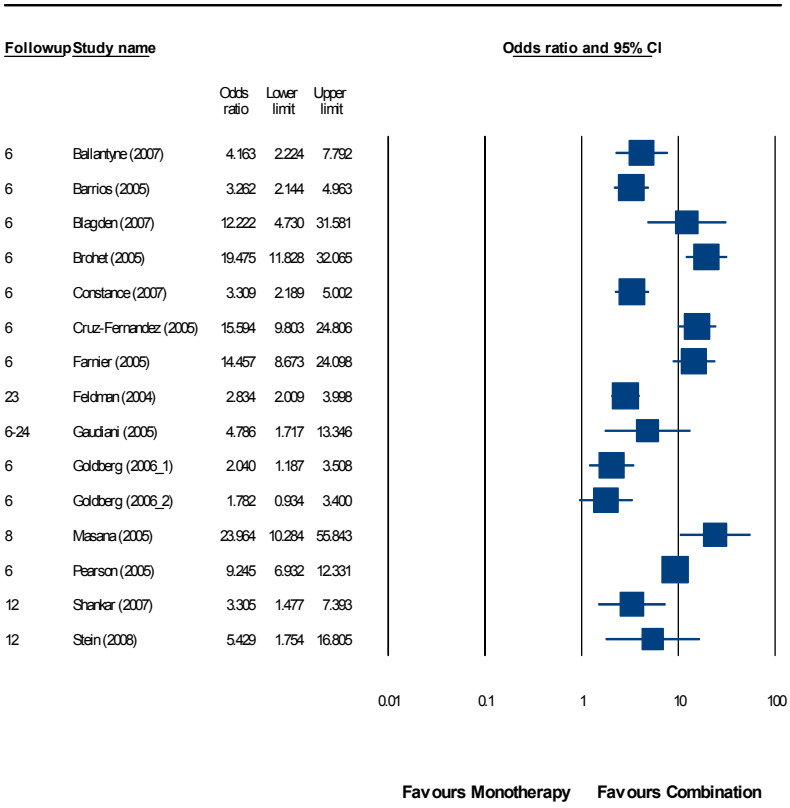
Figure 8 continued



Egger's regression intercept

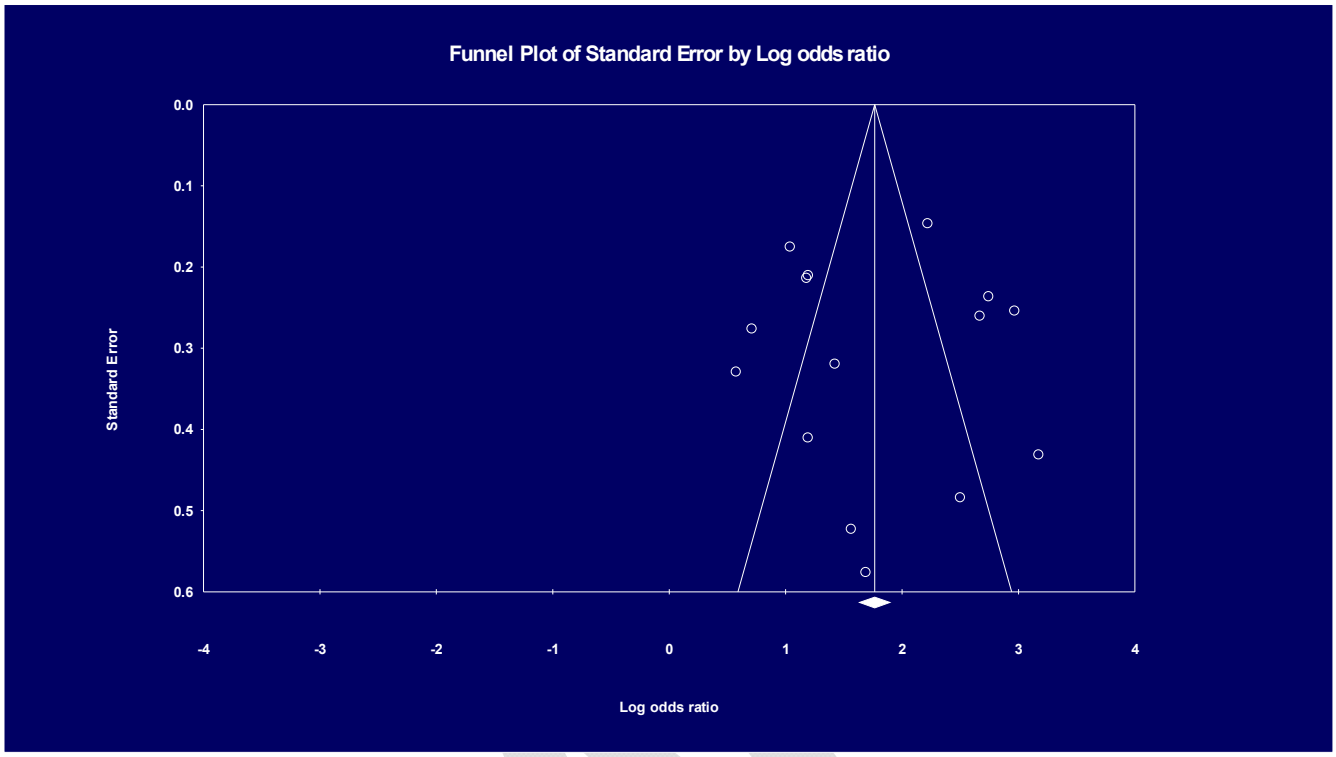
Intercept	-0.51948
Standard error	2.06097
95% lower limit (2-tailed)	-4.81858
95% upper limit (2-tailed)	3.77962
t-value	0.25206
df	20.00000
P-value (1-tailed)	0.40179
P-value (2-tailed)	0.80357

Figure 9. Forest and funnel plots with Egger's regression test, of participants attaining ATP III LDL-c targets for ezetimibe plus statin therapy compared with statin monotherapy in participants requiring intensive lipid lowering therapy



I-squared = 89.76

Figure 9 continued

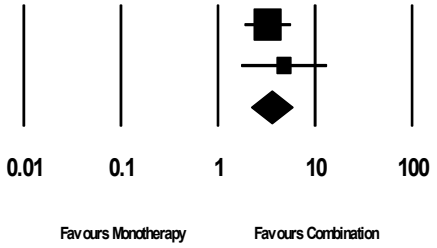


Egger's regression intercept

Intercept	0.17251
Standard error	2.29785
95% lower limit (2-tailed)	-4.79169
95% upper limit (2-tailed)	5.13672
t-value	0.07508
df	13.00000
P-value (1-tailed)	0.47065
P-value (2-tailed)	0.94130

Figure 10. Forest plot of achievement of ATP III LDL-ctargets for lower dose ezetimibe plus simvastatin therapy compared with higher dose simvastatin monotherapy in participants requiring intensive lipid lowering therapy

Followup	Study name	Odds ratio	Lower limit	Upper limit	Events / Total: Combination	Events / Total: Monotherapy
23	Feldman (2004)	3.255	1.867	5.674	90 / 109	147 / 248
6-24	Gaudiani (2005)	4.786	1.717	13.346	28 / 37	13 / 33
		3.553	2.179	5.791		



Model: random effects **I-squared: 0%**

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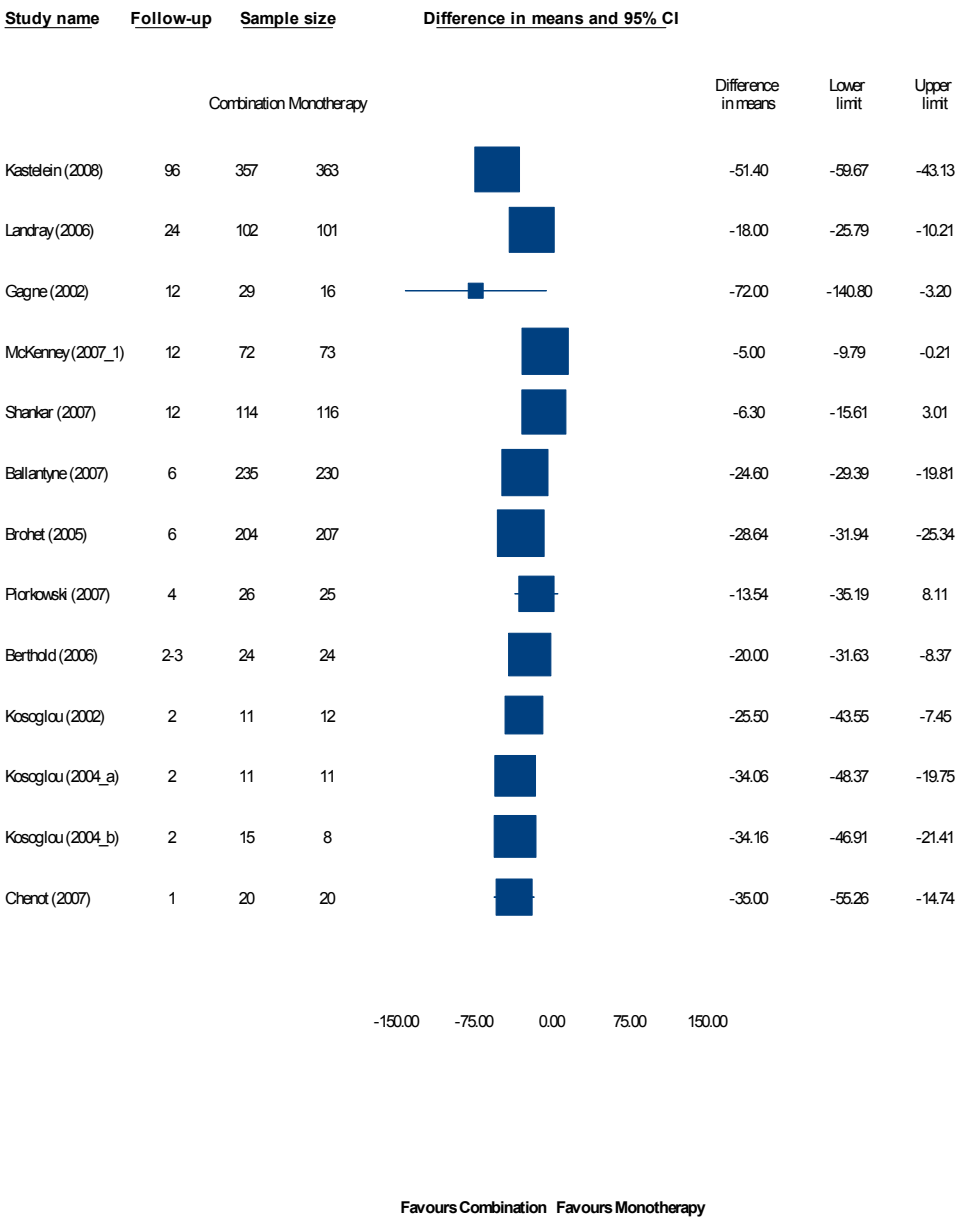
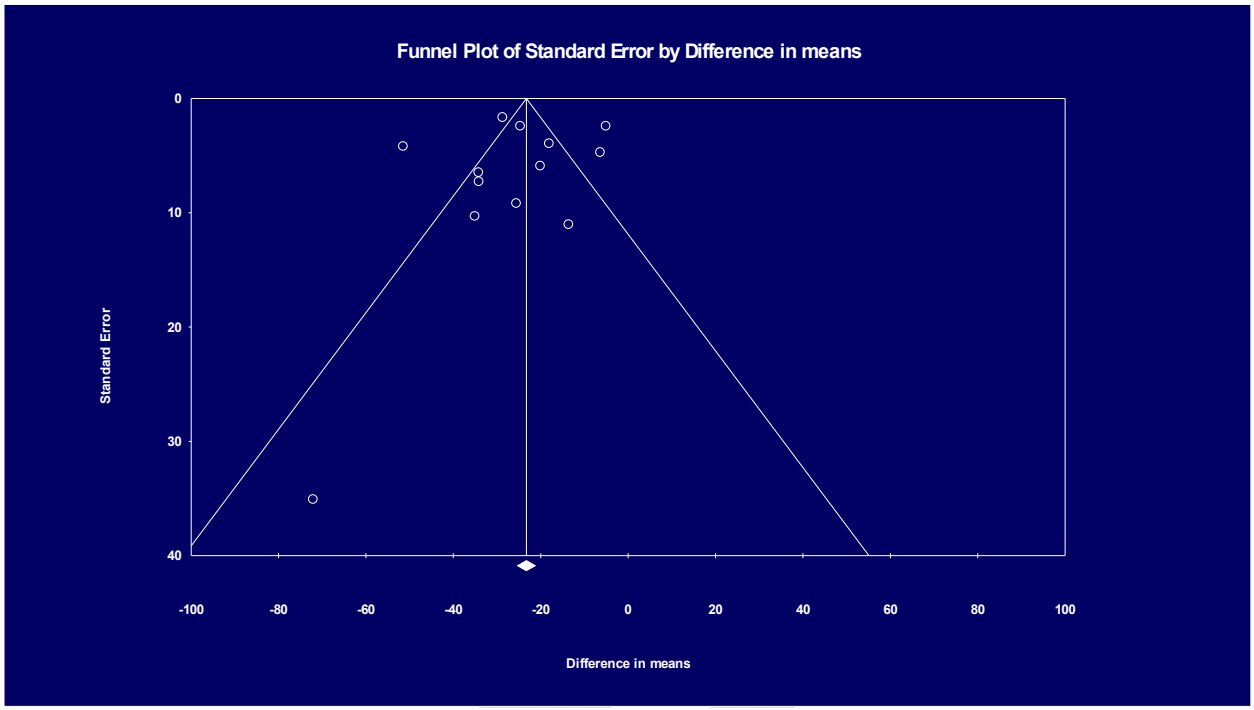
Figure 11. Forest and funnel plots with Egger's regression test, of difference in LDL-c post-treatment means / mean change scores for ezetimibe plus statin therapy compared with statin monotherapy in all participants



I-squared = 91.10

Figure 11 continued



Egger's regression intercept

Intercept	-0.58850
Standard error	1.69831
95% lower limit (2-tailed)	-4.32646
95% upper limit (2-tailed)	3.14946
t-value	0.34652
df	11.00000
P-value (1-tailed)	0.36774
P-value (2-tailed)	0.73549

Figure 12. Forest and funnel plots of difference in LDL-c post-treatment means / mean change scores for ezetimibe plus statin therapy compared with statin monotherapy in participants requiring intensive lipid lowering therapy

Study name	Followup	Sample size		Difference in means and 95% CI			
		Combination	Monotherapy		Difference in means	Lower limit	Upper limit
Kastelein (2008)	96	357	363		-51.400	-59.671	-43.129
Ballantyne (2007)	6	235	230		-24.600	-29.390	-19.810
Brohet (2005)	6	204	207		-28.640	-31.939	-25.341
Piorkowski (2007)	4	26	25		-13.540	-35.194	8.114
Gagne (2002)	12	29	16		-72.000	-140.796	-3.204
Chenot (2007)	1	20	20		-35.000	-55.260	-14.740

-150.00 -75.00 0.00 75.00 150.00

Favours Combination Favours Monotherapy

I-squared = 85.73

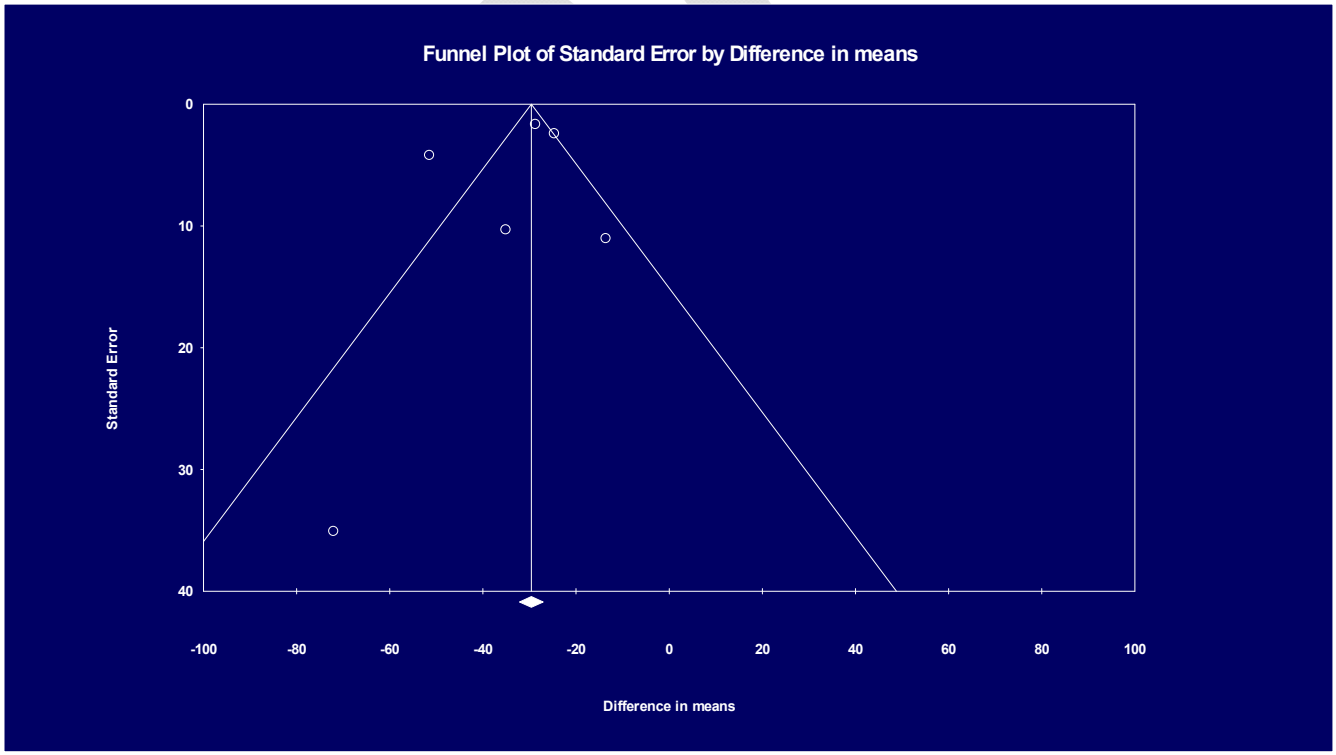


Figure 13. Forest and funnel plots with Egger's regression test of LDL-c difference in mean percentage change from baseline for ezetimibe plus statin therapy compared with statin monotherapy in all participants

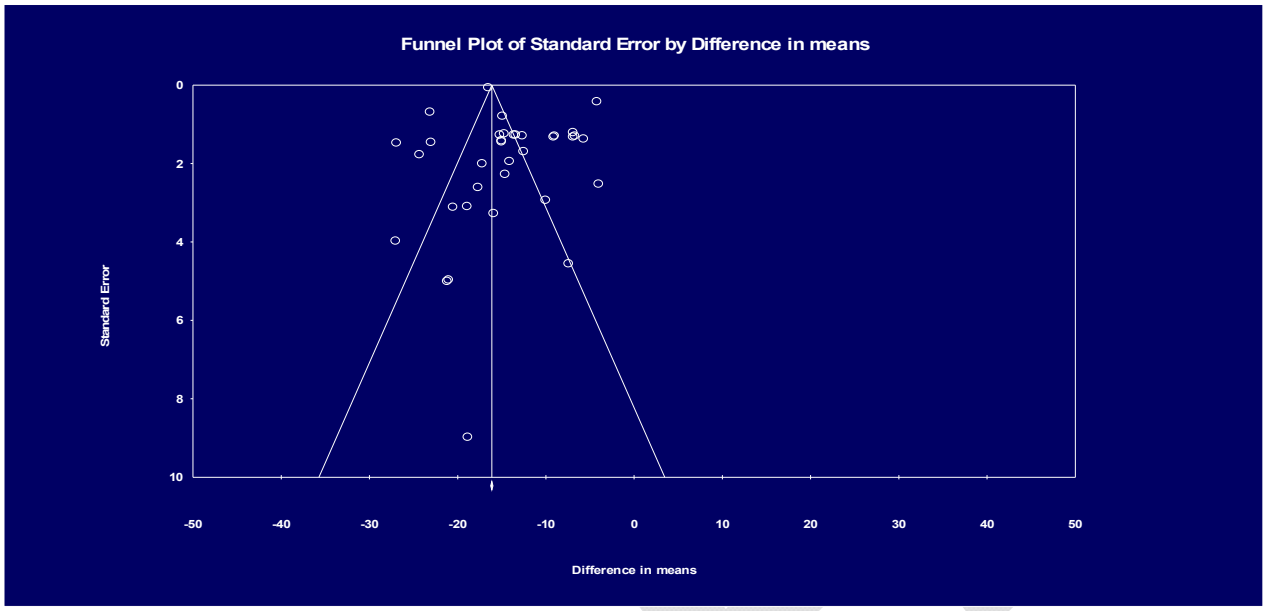
Study name	Follow-up	Sample size		Difference in means and 95% CI			
		Combination	Monotherapy		Difference in means	Lower limit	Upper limit
Kastelein (2008)	96	357	363		-16.50	-16.63	-16.37
Ballantyne (2003)	52	201	45		-10.00	-15.76	-4.24
Landray (2006)	24	102	101		-21.00	-30.74	-11.26
Ballantyne (2004_b)	24	432	223		-6.90	-9.27	-4.53
Stein (2004)	14	278	290		-13.60	-16.10	-11.10
Rodney (2006)	12	124	123		-17.20	-21.13	-13.27
Masana (2005)	12	344	78		-27.00	-34.80	-19.20
Goldberg (2004)	12	323	322		-14.70	-17.13	-12.27
Melani (2003)	12	204	205		-13.40	-15.89	-10.91
Kerzner (2003)	12	181	202		-15.00	-17.78	-12.22
Davidson (2002)	12	253	249		-15.20	-17.70	-12.70
Gagne (2002_1)	12	12	12		-21.16	-30.97	-11.35
Gagne (2002_2)	12	5	5		-18.83	-36.43	-1.23
McKenney (2007_1)	12	72	73		-4.00	-8.95	0.95
Shankar (2007)	12	114	116		-7.40	-16.33	1.53
Barrios (2005)	6	215	207		-12.50	-15.83	-9.17
Farnier (2005)	6	102	101		-24.30	-27.78	-20.82
Cruz-Fernandez (2005)	6	219	224		-26.90	-29.80	-24.00
Brohet (2005)	6	204	207		-23.00	-25.86	-20.14
Pearson (2005)	6	1940	968		-23.10	-24.45	-21.75
Ballantyne (2005_1)	6	233	230		-6.90	-9.49	-4.31
Ballantyne (2005_2)	6	236	232		-9.10	-11.69	-6.51
Ballantyne (2005_3)	6	224	230		-5.70	-8.39	-3.01
Gaudiani (2005)	6-24	103	107		-20.50	-26.60	-14.40
Blagden (2007)	6	72	76		-14.10	-17.92	-10.28
Ballantyne (2007)	6	235	230		-12.64	-15.18	-10.10
Patel (2006)	6	72	71		-14.60	-19.06	-10.14
Goldberg (2006_1)	6	238	240		-9.00	-11.55	-6.45
Goldberg (2006_2)	6	242	241		-6.70	-9.25	-4.15
Catapano (2006)	6	1427	1428		-4.20	-5.03	-3.37
Constance (2007)	6	210	213		-17.66	-22.78	-12.54
Feldman (2004)	5	108	246		-15.00	-17.83	-12.17
Bays (2004)	4-26	539	559		-14.90	-16.46	-13.34
Kosoglou (2004)	2	11	11		-15.90	-22.32	-9.48
Berthold (2006)	2-3	24	24		-18.90	-24.97	-12.83

-40.00 -20.00 0.00 20.00 40.00

Favours Combination Favours Monotherapy

I-squared = 97.51

Figure 13 continued

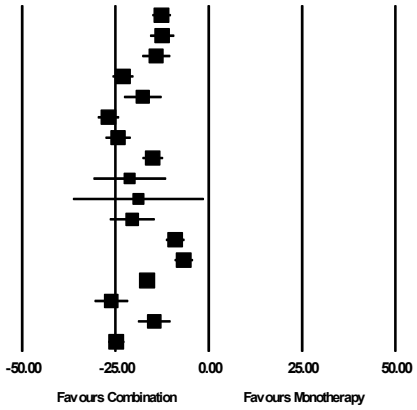


Egger's regression intercept

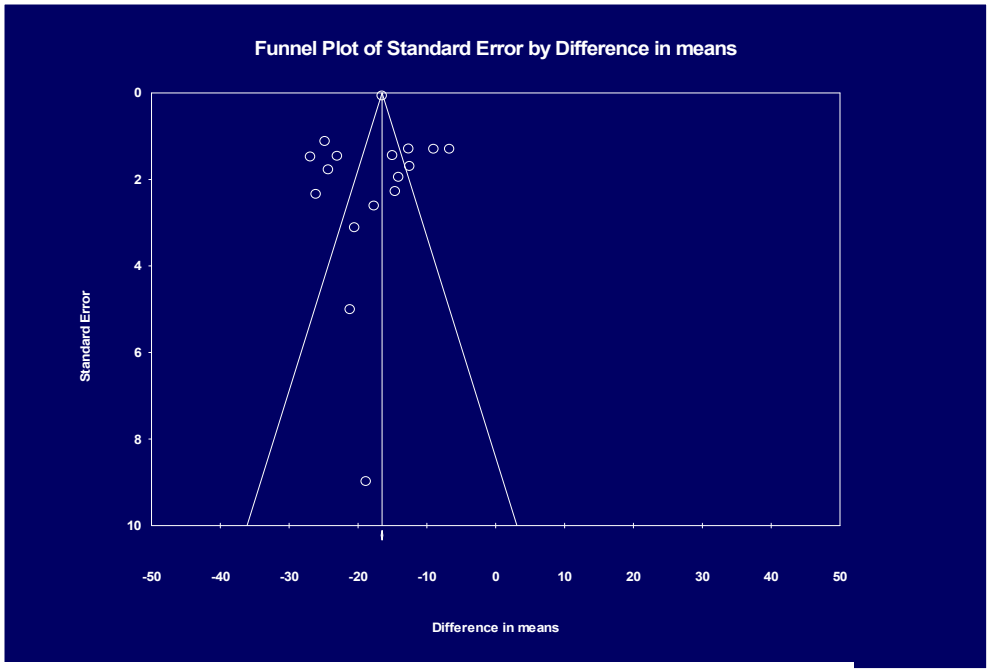
Intercept	1.76816
Standard error	1.14695
95% lower limit (2-tailed)	-0.56532
95% upper limit (2-tailed)	4.10163
t-value	1.54162
df	33.00000
P-value (1-tailed)	0.06635
P-value (2-tailed)	0.13270

Figure 14. Forest and funnel plots with Egger's regression test, of LDL-c difference in mean percentage change from baseline for ezetimibe plus statin therapy compared with statin monotherapy in participants requiring intensive lipid lowering therapy

Followup	Studyname	Statistics for each study				Sample size	
		Difference in means	Standard error	Lower limit	Upper limit	Combination	Monotherapy
6	Ballantyne (2007)	-12.640	1.294	-15.176	-10.104	235	230
6	Barrios (2005)	-12.500	1.698	-15.827	-9.173	215	207
6	Blagden (2007)	-14.100	1.948	-17.918	-10.282	72	76
6	Brohet (2005)	-23.000	1.461	-25.864	-20.136	204	207
6	Constance (2007)	-17.660	2.612	-22.779	-12.541	210	213
6	Cruz-Fernandez (2005)	-26.900	1.478	-29.796	-24.004	219	224
6	Farnier (2005)	-24.300	1.775	-27.779	-20.821	102	101
5	Feldman (2004)	-15.000	1.446	-17.834	-12.166	108	246
12	Gagne (2002_1)	-21.160	5.005	-30.970	-11.350	12	12
12	Gagne (2002_2)	-18.830	8.981	-36.432	-1.228	5	5
6_24	Gaudiani (2005)	-20.500	3.114	-26.603	-14.397	103	107
6	Goldberg (2006_1)	-9.000	1.299	-11.546	-6.454	238	240
6	Goldberg (2006_2)	-6.700	1.299	-9.246	-4.154	242	241
96	Kastelein (2008)	-16.500	0.067	-16.631	-16.369	357	363
8	Masana (2005)	-26.100	2.342	-30.690	-21.510	88	94
6	Patel (2006)	-14.600	2.276	-19.061	-10.139	72	71
6	Pearson (2005)	-24.800	1.120	-26.995	-22.605	739	387



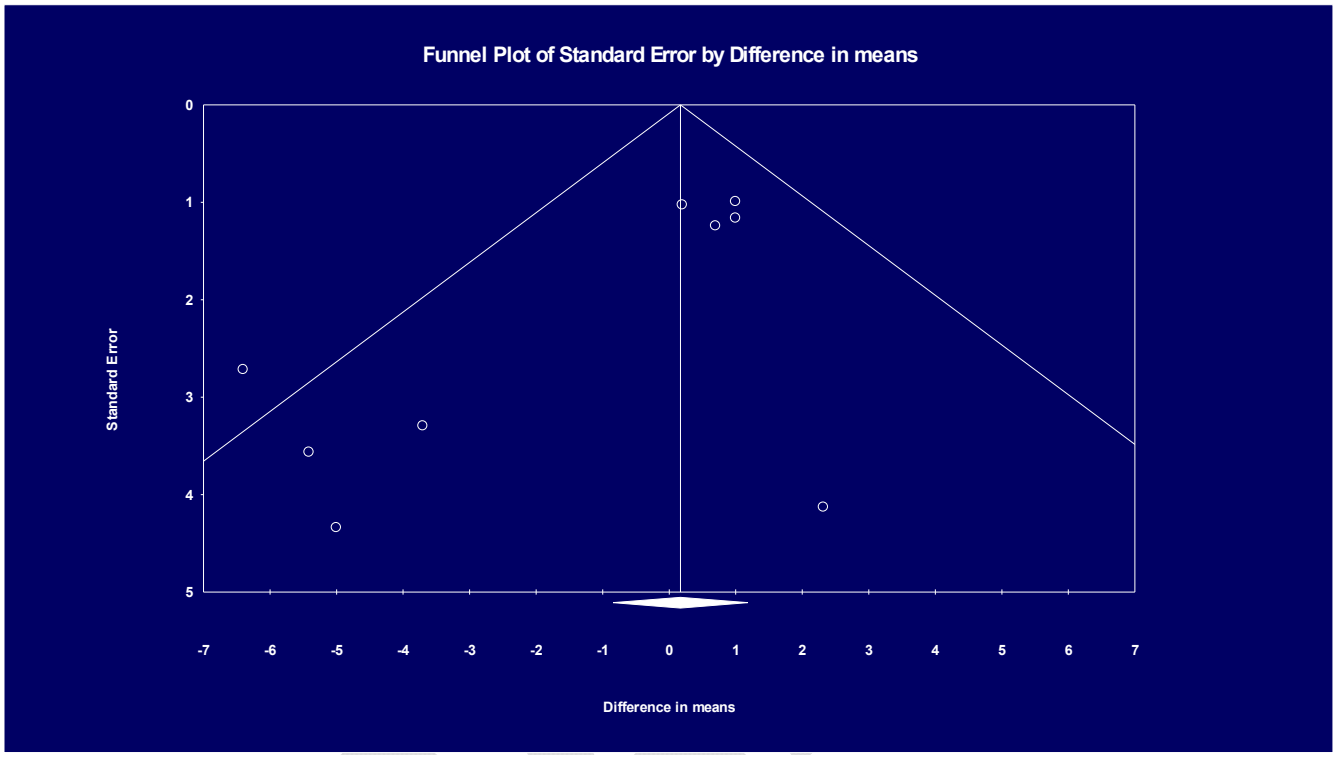
Model: random effects **I-squared: 94.1%**



Egger's regression intercept

Intercept	-0.56121
Standard error	1.10569
95% lower limit (2-tailed)	-2.91793
95% upper limit (2-tailed)	1.79551
t-value	0.50757
df	15.00000
P-value (1-tailed)	0.30957
P-value (2-tailed)	0.61914

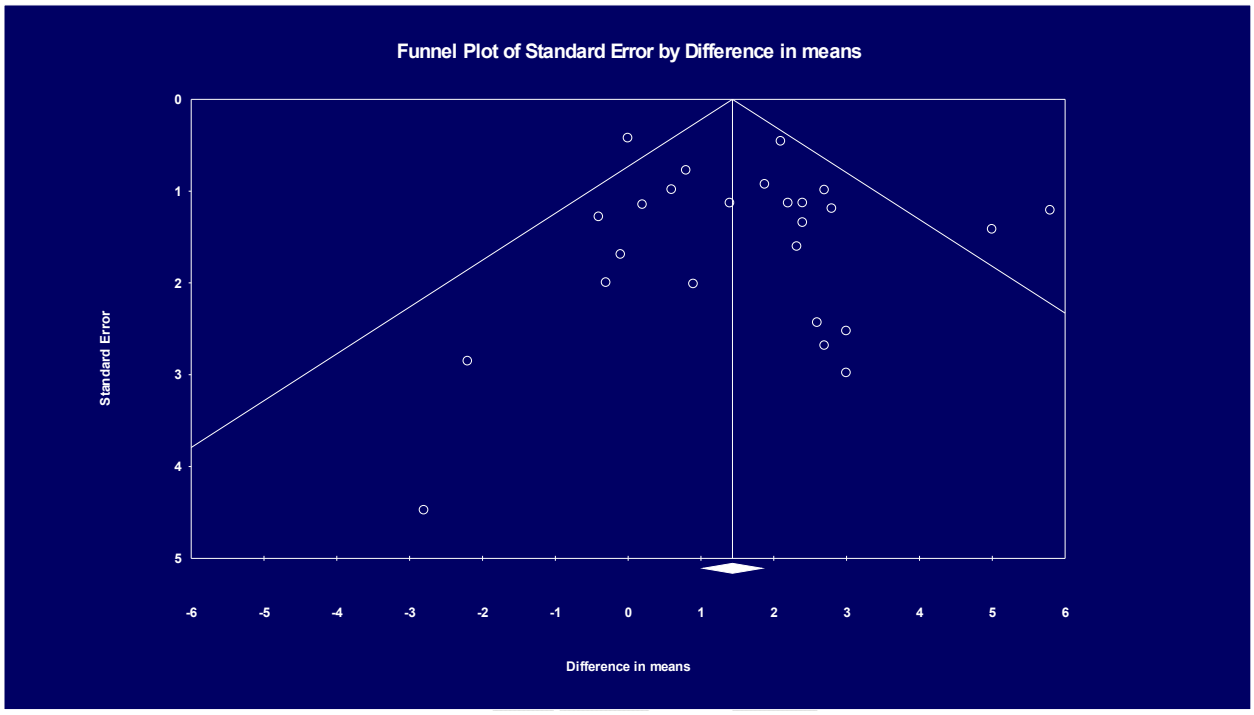
Figure 15. Funnel plot with Egger's regression test of difference in HDL-c post-treatment means / mean change scores for ezetimibe plus statin therapy compared with statin monotherapy in all participants



Egger's regression intercept

Intercept	-1.75211
Standard error	0.63111
95% lower limit (2-tailed)	-3.24445
95% upper limit (2-tailed)	-0.25977
t-value	2.77623
df	7.00000
P-value (1-tailed)	0.01372
P-value (2-tailed)	0.02745

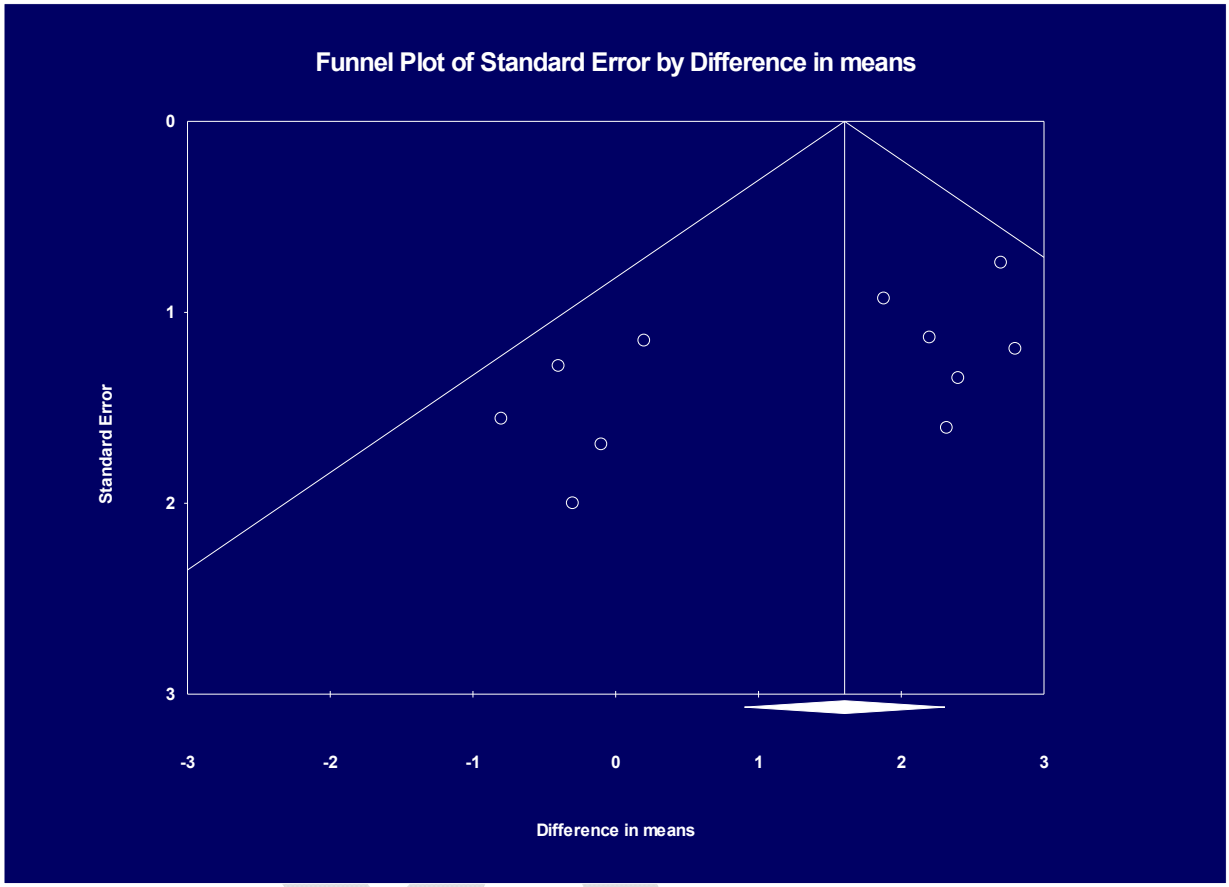
Figure 16. Funnel plot with Egger's regression test of difference in HDL-c percentage change from baseline for ezetimibe plus statin therapy compared with statin monotherapy in all participants



Egger's regression intercept

Intercept	0.52763
Standard error	0.54603
95% lower limit (2-tailed)	-0.60191
95% upper limit (2-tailed)	1.65717
t-value	0.96631
df	23.00000
P-value (1-tailed)	0.17197
P-value (2-tailed)	0.34394

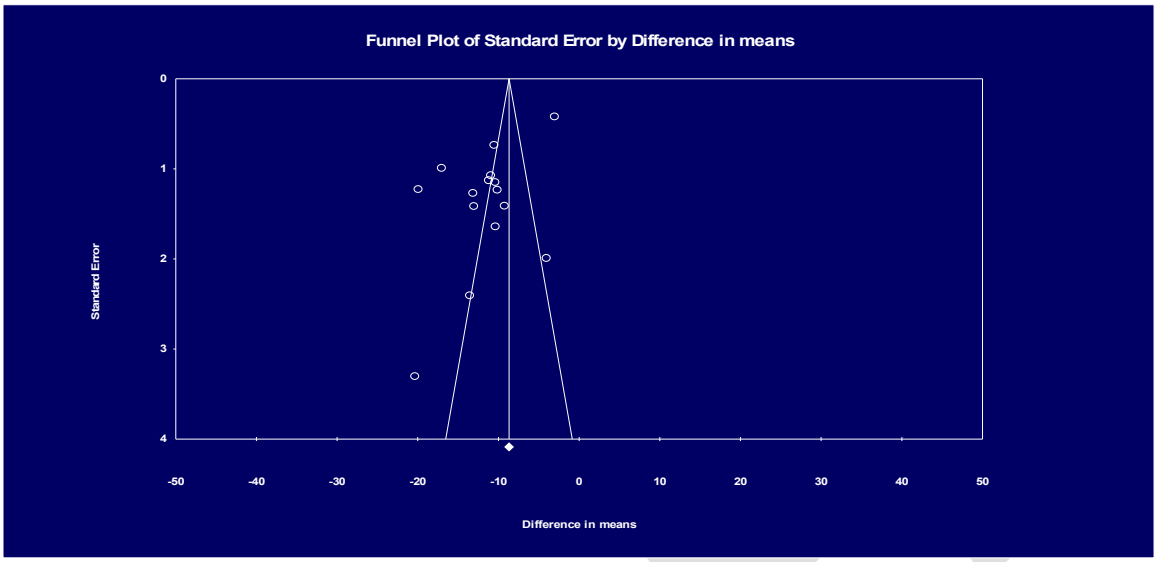
Figure 17. Funnel plot with Egger's regression test of difference in HDL-c percentage change from baseline for ezetimibe plus statin therapy compared with statin monotherapy in participants requiring intensive lipid lowering therapy



Egger's regression intercept

Intercept	-2.34485
Standard error	1.02312
95% lower limit (2-tailed)	-4.65930
95% upper limit (2-tailed)	-0.03039
t-value	2.29187
df	9.00000
P-value (1-tailed)	0.02381
P-value (2-tailed)	0.04763

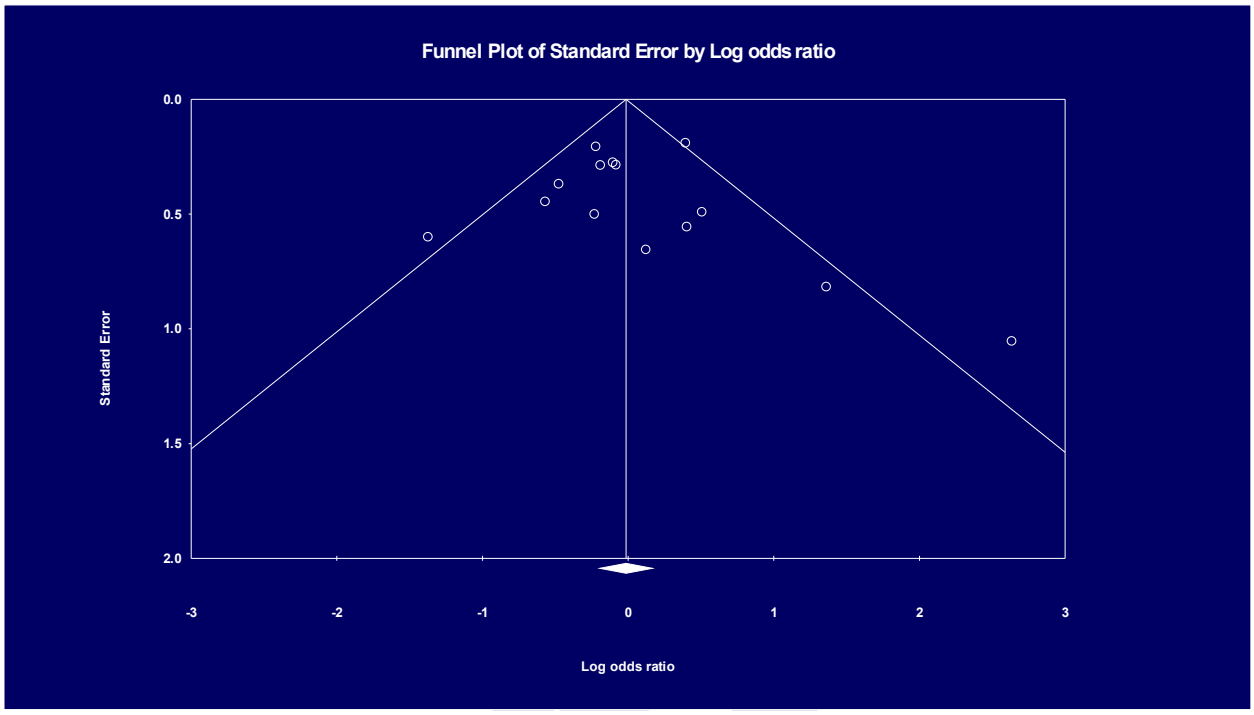
Figure 18. Funnel plot with Egger's regression test of difference in total cholesterol:HDL-c (ratio) percentage change from baseline for ezetimibe plus statin therapy compared with statin monotherapy in all participants



Egger's regression intercept

Intercept	-7.26531
Standard error	2.23594
95% lower limit (2-tailed)	-12.09576
95% upper limit (2-tailed)	-2.43486
t-value	3.24933
df	13.00000
P-value (1-tailed)	0.00317
P-value (2-tailed)	0.00634

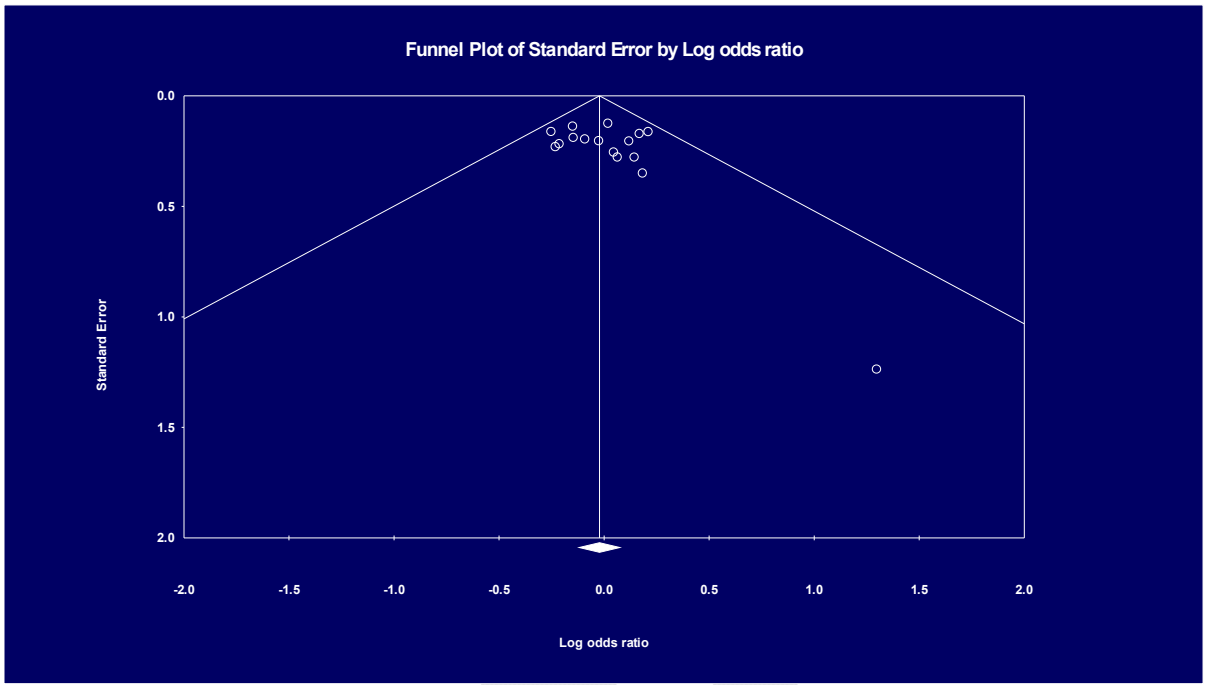
Figure 19. Funnel plot with Egger's regression test of treatment adherence, for ezetimibe plus statin therapy compared with statin monotherapy in all participants



Egger's regression intercept

Intercept	0.41330
Standard error	0.88404
95% lower limit (2-tailed)	-1.51285
95% upper limit (2-tailed)	2.33945
t-value	0.46752
df	12.00000
P-value (1-tailed)	0.32425
P-value (2-tailed)	0.64851

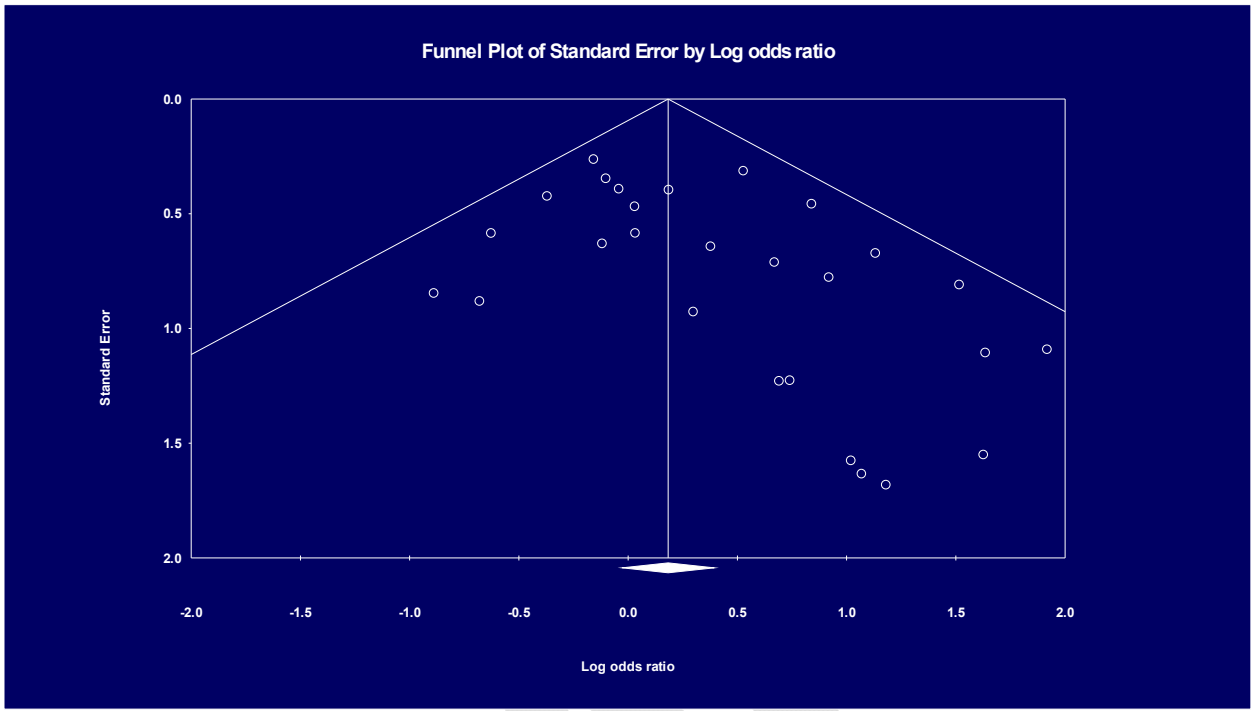
Figure 20. Funnel plot with Egger's regression test of proportion of participants with at least one adverse event, for ezetimibe plus statin therapy compared with statin monotherapy in all participants



Egger's regression intercept

Intercept	0.78989
Standard error	0.63459
95% lower limit (2-tailed)	-0.57116
95% upper limit (2-tailed)	2.15094
t-value	1.24473
df	14.00000
P-value (1-tailed)	0.11683
P-value (2-tailed)	0.23367

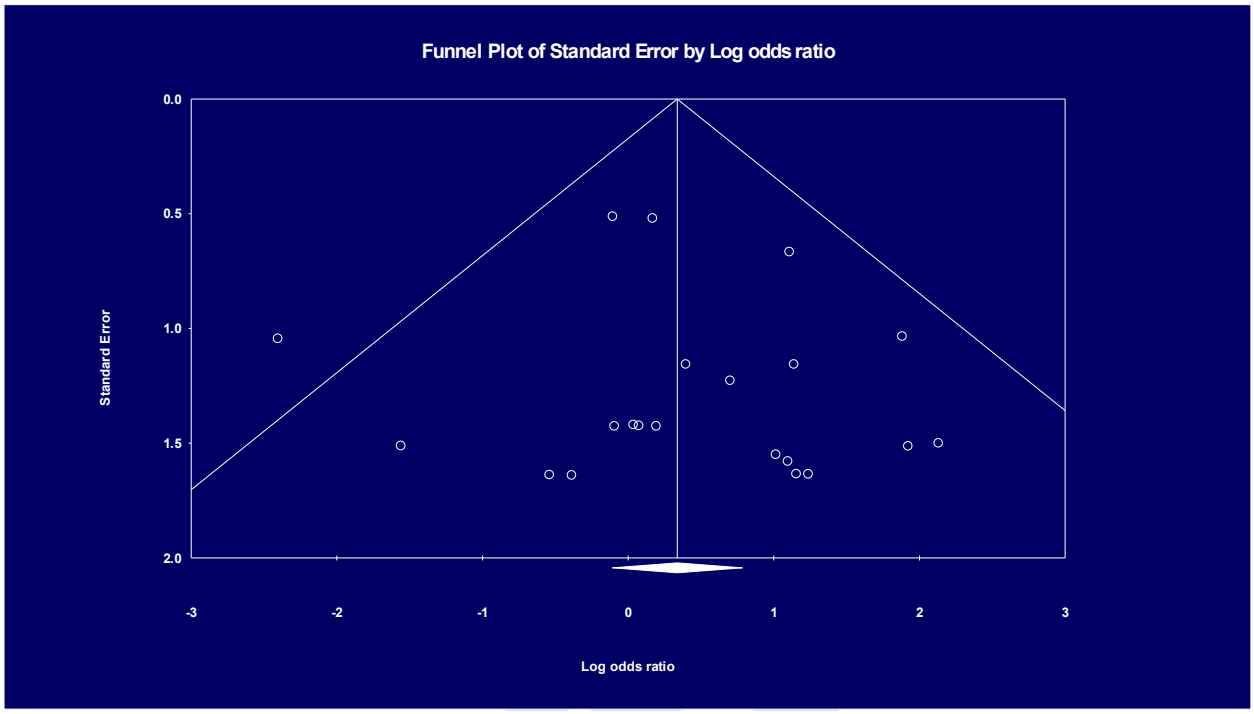
Figure 21. Funnel plot with Egger's regression test of proportion of participants withdrawing from treatment due to an adverse event, for ezetimibe plus statin therapy compared with statin monotherapy in all participants



Egger's regression intercept

Intercept	0.92267
Standard error	0.37009
95% lower limit (2-tailed)	0.16045
95% upper limit (2-tailed)	1.68488
t-value	2.49309
df	25.00000
P-value (1-tailed)	0.00982
P-value (2-tailed)	0.01965

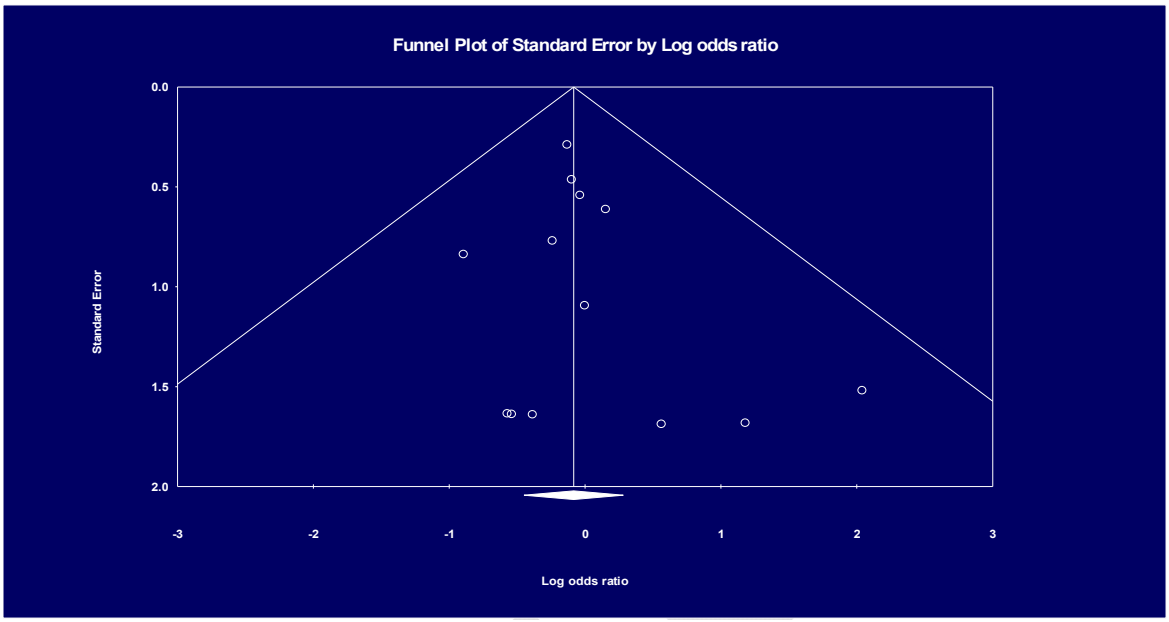
Figure 22. Funnel plot with Egger's regression test of proportion of participants with AST and/or ALT above 3 times the upper limit of normal, and/or hepatitis, for ezetimibe plus statin therapy compared with statin monotherapy in all participants



Egger's regression intercept

Intercept	0.30224
Standard error	0.50349
95% lower limit (2-tailed)	-0.75157
95% upper limit (2-tailed)	1.35605
t-value	0.60029
df	19.00000
P-value (1-tailed)	0.27770
P-value (2-tailed)	0.55540

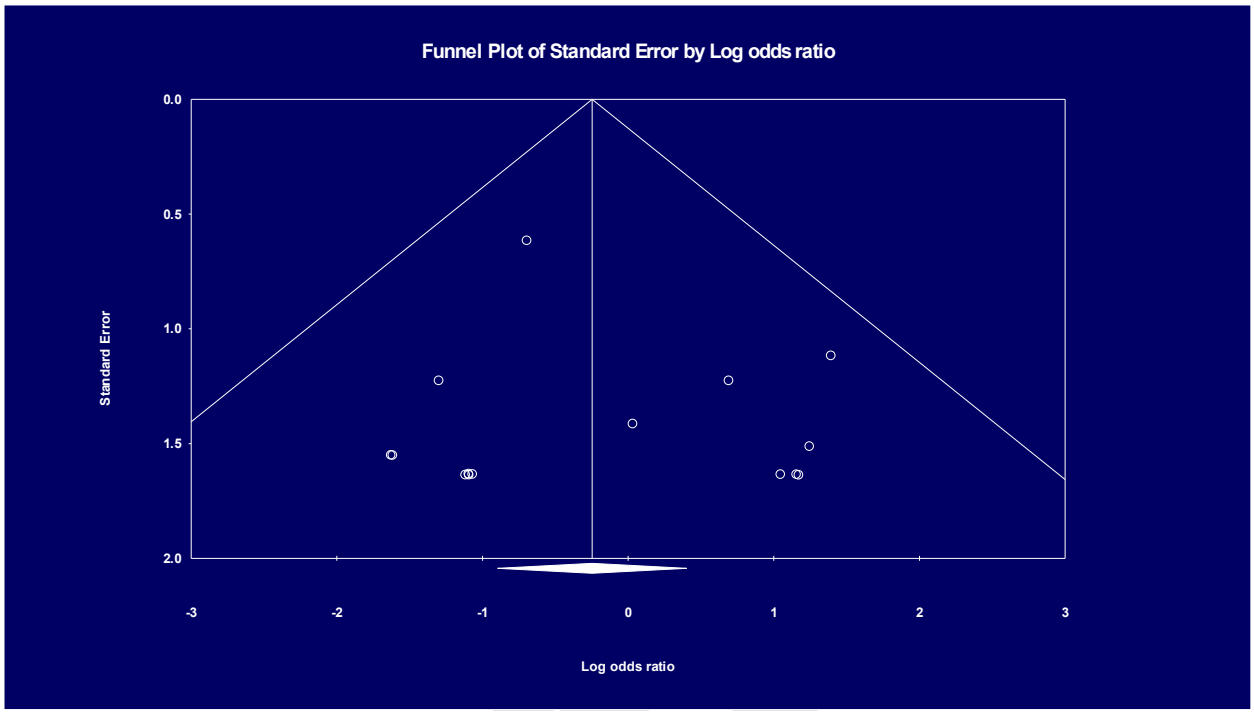
Figure 23. Funnel plot with Egger's regression test of proportion of participants experiencing myalgia, for ezetimibe plus statin therapy compared with statin monotherapy in all participants



Egger's regression intercept

Intercept	0.25138
Standard error	0.29570
95% lower limit (2-tailed)	-0.39944
95% upper limit (2-tailed)	0.90221
t-value	0.85013
df	11.00000
P-value (1-tailed)	0.20669
P-value (2-tailed)	0.41337

Figure 24. Funnel plot with Egger's regression test of proportion of participants with CPK above 10 times the upper limit of normal, for ezetimibe plus statin therapy compared with statin monotherapy in all participants

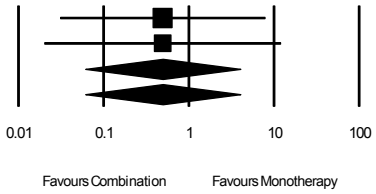


Egger's regression intercept

Intercept	0.33868
Standard error	0.68625
95% lower limit (2-tailed)	-1.14387
95% upper limit (2-tailed)	1.82124
t-value	0.49353
df	13.00000
P-value (1-tailed)	0.31494
P-value (2-tailed)	0.62987

Figure 25. Forest plot of all-cause mortality for ezetimibe plus statin therapy compared with statin monotherapy in participants with diabetes mellitus

Group by Allocation concealment	Study name	Odds ratio	Lower limit	Upper limit	Events / Total: Combination	Events / Total: Monotherapy
ADEQUATE	Constance (2007)	0.494	0.031	7.941	1 / 442	1 / 219
ADEQUATE	Goldberg (2006)	0.493	0.020	12.129	0 / 494	1 / 732
ADEQUATE		0.494	0.061	4.024		
Overall		0.494	0.061	4.024		



Sensitivity analysis according to allocation concealment Model: random effects I-squared = 0%

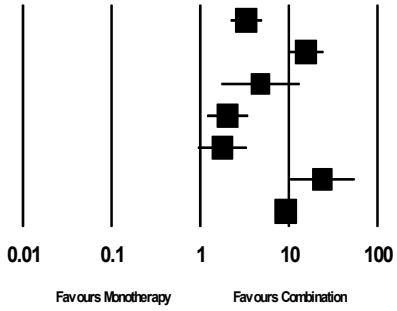
Figure 26. Forest plot of all-cause mortality for ezetimibe plus statin therapy compared with statin monotherapy in participants with established vascular disease

Study name	Odds ratio	Lower limit	Upper limit	Events / Total: Combination	Events / Total: Monotherapy
Cruz-Fernandez (2005)	0.347	0.014	8.562	0 / 220	1 / 230
Patel (2006)	0.325	0.013	8.096	0 / 76	1 / 75
	0.336	0.035	3.251		

Model: random effects I-squared: 0%

Figure 27. Forest and funnel plots of achievement of achievement of ATP III LDL-c targets for ezetimibe plus statin therapy compared with statin monotherapy in participants with diabetes mellitus

Followup	Study name	Odds ratio	Lower limit	Upper limit	Events / Total Combination	Events / Total Monotherapy
6	Constance (2007)	3.309	2.189	5.002	392 / 442	154 / 219
6	Cruz-Fernandez (2005)	15.594	9.803	24.806	178 / 219	49 / 225
6-24	Gaudiani (2005)	4.786	1.717	13.346	28 / 37	13 / 33
6	Goldberg (2006_1)	2.040	1.187	3.508	215 / 238	197 / 240
6	Goldberg (2006_2)	1.782	0.934	3.400	226 / 242	214 / 241
8	Masana (2005)	23.964	10.284	55.843	61 / 73	14 / 80
6	Pearson (2005)	9.245	6.932	12.331	546 / 768	83 / 395



Model: random effects **I-squared: 91.67%**

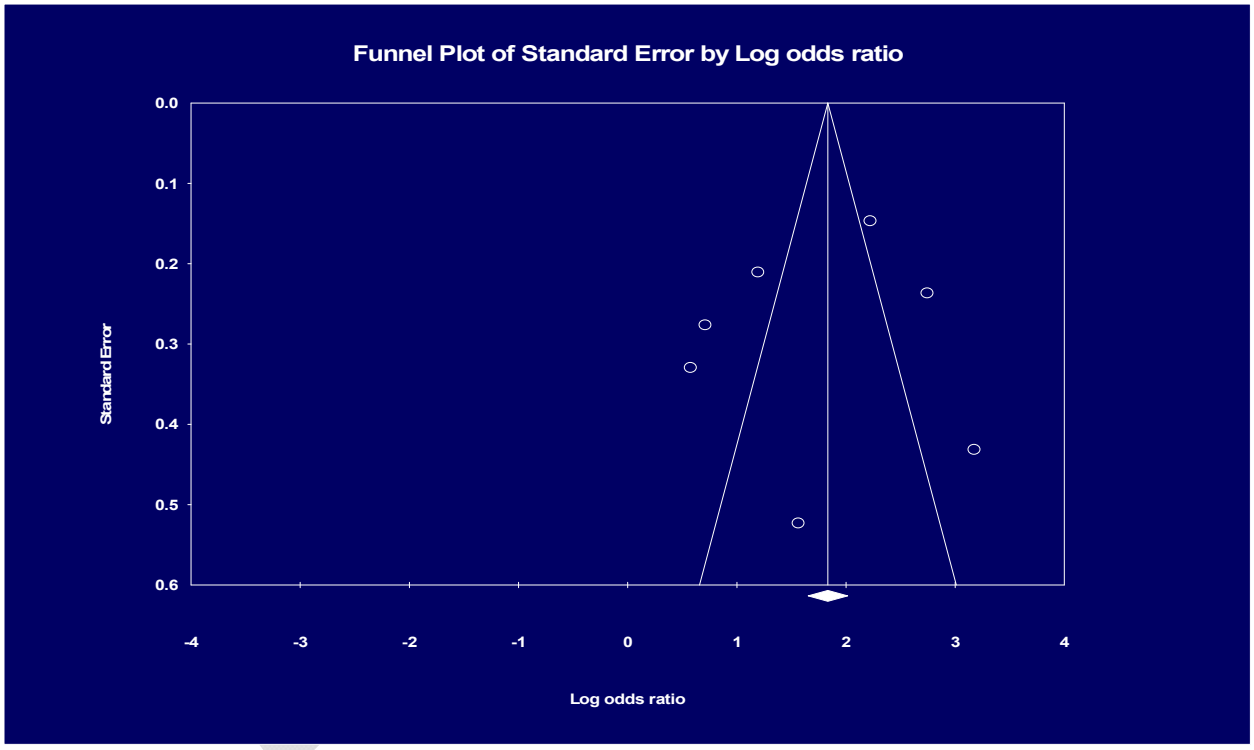
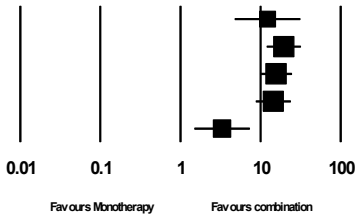


Figure 28. Forest plot of achievement of ATP III LDL-c targets for ezetimibe plus statin therapy compared with statin monotherapy in participants with established vascular disease

Sub-group: Proportion of participants rwith established vascualr diseases reaching LDL-c ATPIII targets **Comparison: Statins+Ezetimibe vs. Statins**

Followup	Study name	Odds ratio	Lower limit	Upper limit	Events / Total Combination	Events / Total Monotherapy
6	Blagden (2007)	12.222	4.730	31.581	66 / 72	36 / 76
6	Brohet (2005)	19.475	11.828	32.065	164 / 204	36 / 207
6	Cruz-Fernandez (2005)	15.594	9.803	24.806	178 / 219	49 / 225
6	Farnier (2005)	14.457	8.673	24.098	133 / 179	31 / 186
12	Shankar (2007)	3.305	1.477	7.393	75 / 85	59 / 85

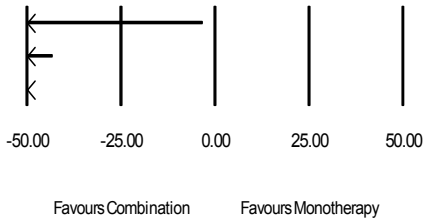


Model: random effects **I-squared: 72%**

DRAFT

Figure 29. Forest plot of LDL-c difference in post-treatment means / mean change scores for ezetimibe plus statin therapy compared with statin monotherapy in participants with baseline LDL-c above 190 mg/dL

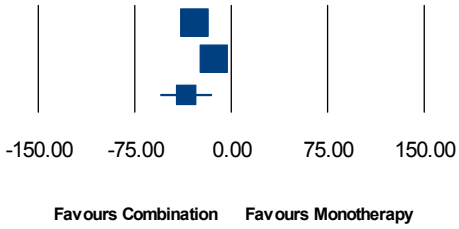
Followup	Study name	Statistics for each study				Sample size	
		Difference in means	Standard error	Lower limit	Upper limit	Combination	Monotherapy
12	Gagne (2002)	-72.00	35.10	-140.80	-3.20	29	16
96	Kastelein (2008)	-51.40	4.22	-59.67	-43.13	357	363
		-51.69	4.19	-59.91	-43.48		



Model: random effects I-squared = 0%

Figure 30. Forest plot of LDL-c difference in post-treatment means / mean change scores for ezetimibe plus statin therapy compared with statin monotherapy in participants with established vascular disease

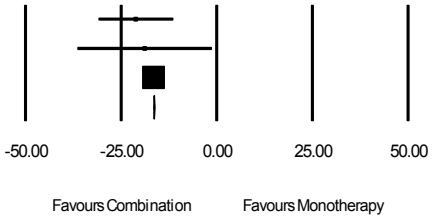
Study name	Followup	Sample size		Difference in means	Lower limit	Upper limit
		Combination	Monotherapy			
Brohet (2005)	6	204	207	-28.640	-31.939	-25.341
Piorkowski (2007)	4	26	25	-13.540	-17.819	-9.261
Chenot (2007)	1	20	20	-35.000	-55.260	-14.740



I-squared = 93.62

Figure 31. Forest plot of LDL-c difference in mean percentage change from baseline, for ezetimibe plus statin therapy compared with statin monotherapy in participants with baseline LDL-c above 190 mg/dL

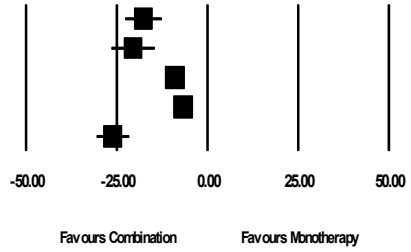
Followup	Study name	Statistics for each study				Sample size	
		Difference in means	Standard error	Lower limit	Upper limit	Combination	Monotherapy
12	Gagne (2002_1)	-21.16	5.01	-30.97	-11.35	12	12
12	Gagne (2002_2)	-18.83	8.98	-36.43	-1.23	5	5
96	Kastelein (2008)	-16.50	0.07	-16.63	-16.37	357	363
		-16.50	0.07	-16.63	-16.37		



Model: random effects I-squared = 0%

Figure 32. Forest plot of LDL-c difference in mean percentage change from baseline, for ezetimibe plus statin therapy compared with statin monotherapy in participants with diabetes mellitus

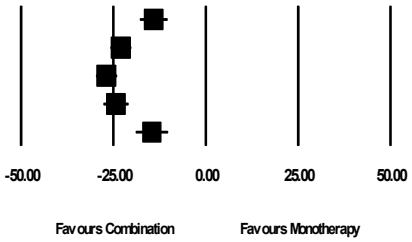
Followup	Studyname	Statistics for each study				Sample size	
		Difference in means	Standard error	Lower limit	Upper limit	Combination	Monotherapy
6	Constance (2007)	-17.660	2.612	-22.779	-12.541	210	213
6_24	Gaudiani (2005)	-20.500	3.114	-26.603	-14.397	103	107
6	Goldberg (2006_1)	-9.000	1.299	-11.546	-6.454	238	240
6	Goldberg (2006_2)	-6.700	1.299	-9.246	-4.154	242	241
8	Masana (2005)	-26.100	2.342	-30.690	-21.510	88	94



Model: random effects I-squared: 94.3%

Figure 33. Forest plot of LDL-c difference in mean percentage change from baseline, for ezetimibe plus statin therapy compared with statin monotherapy in participants with established vascular disease

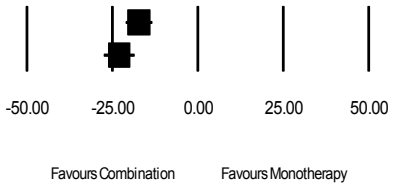
Followup	Study name	Statistics for each study				Sample size	
		Difference in means	Standard error	Lower limit	Upper limit	Combination	Monotherapy
6	Blagden (2007)	-14.100	1.948	-17.918	-10.282	72	76
6	Brohet (2005)	-23.000	1.461	-25.864	-20.136	204	207
6	Cruz-Fernandez (2005)	-26.900	1.478	-29.796	-24.004	219	224
6	Farnier (2005)	-24.300	1.775	-27.779	-20.821	102	101
6	Patel (2006)	-14.600	2.276	-19.061	-10.139	72	71



Model: random effects **I-squared: 90%**

Figure 34. Forest plot of LDL-c difference in mean percentage change from baseline, for ezetimibe plus statin therapy compared with statin monotherapy in participants of African descent

Followup	Study name	Statistics for each study				Sample size	
		Difference in means	Standard error	Lower limit	Upper limit	Combination	Monotherapy
12	Rodney (2006)	-17.20	2.01	-21.13	-13.27	124	124
6	Pearson (2005)	-23.00	2.32	-27.55	-18.45	174	93



Model: random effects **I-squared = 72%**

Fibrate Combination Therapy versus Statin Monotherapy

Overview of included studies

A total of 11 randomized controlled trials evaluated the relative efficacy and/or harms of the combination of statins plus fibrates (fenofibrate 67-200mg/day, gemfibrozil 1200 mg/day) versus statin monotherapy in a total of 1991 participants (Table 4).[41,105,115,118,121,129,142,143,167,171,174] One included non-randomized study addressed this particular comparison (Table 16).[78] Two randomized trials had one or more companion reports of the same trial (Table 6).[142,199] Data from the report with the longest available duration were used for analysis, and one of the companion reports was considered for trial referencing.

Three trials were conducted in multiple centers,[105,115,121] and five in a single centre,[41,129,167,171,174] while this information was not reported for three trials.[118,142,143] Three of 11 trials were partially or completely sponsored by the pharmaceutical industry,[105,121,129] one study explicitly reported being conducted independently of industry funding,[142] and reports of seven trials did not disclose funding sources.[41,115,118,143,167,171,174] Total Jadad scores for trials ranged from one to three. Two trials were reported to be appropriately randomized,[41,142] while five used an appropriate method for double blinding.[105,115,118,129,171] Allocation concealment was adequate in two trials [41,142] and five trials used intention-to-treat analysis.[118,129,142,143,171]

Trials were distributed by geographical region as follows:

- North America - two trials [115,129]
- Europe - eight trials [41,105,118,121,142,143,167,171]
- Asia - one trial [174]

Reporting of participants' ethnicity was provided in three trials as follows:

- European descent (97 to 100%)[115,118,121]
- Hispanic descent (6.5%)[115]
- African descent (2.8%)[115]

Power analyses regarding the primary outcome measures were reported for no trials, and except for three trials,[105,167,171] active clinical adverse event data collection was either not reported or unclear.

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 co-administration of different lipid-modifying agents (i.e. a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

DRAFT

One or more clinical outcomes or serious adverse events were reported for five trials, none using crossover design, that randomized 990 participants to compare statins plus fibrates with statin monotherapy (Table 15).[105,115,118,121,167]

Three trials provided information on participants' descent, with a mean of 90-100% of participants of European descent,[115,118,121] 2.8% of African descent,[115] and 6.5% of Hispanic descent.[115]

No trial was conducted exclusively in a single gender. On average, 45% of participants were female (range 33 to 50%). The average of mean ages of participants was 55 years (range of mean ages, 49 to 60 years). Three trials recruited outpatients,[105,121,167] while two trials did not report recruitment setting. The mean Jadad score was 2 (range, 1 to 3) and one trial had adequate allocation concealment.[115] Two trials were exclusively in participants requiring intensive lipid lowering treatment (i.e. participants with established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL).[105,121] These two trials randomized 297 participants.

Participants in these five trials were of heterogeneous characteristics, including those with familial combined hypercholesterolemia,[115,167] diabetes mellitus,[121] established vascular disease and/or CHD risk equivalent and/or diabetes mellitus,[118] and prior statin exposure.[115,118] Most trials excluded participants with triglycerides above 300-600 mg/dL, patients with recent or unstable vascular disease, uncontrolled diabetes mellitus and hypertension, liver or muscle disease or high ALT, AST or CPK, or impaired renal function. No trial reported employing a fibrate-statin combination as a combined pill.

Outcomes without evidence

No randomized controlled trial rigorously reported the following outcomes: vascular death, cerebrovascular events, ischemic stroke, hemorrhagic stroke, transient ischemic attack, carotid endarterectomy, percutaneous coronary intervention, coronary arterial bypass graft or any revascularization procedure, or cancer.

DRAFT

Longer term efficacy and serious adverse events

All-cause mortality: fibrate-statin combination versus statin monotherapy

Key Point

- A single small trial compared groups for a period greater than 24 weeks and reported no deaths. No significant difference in mortality is noted pooling all evaluable patients irrespective of followup period, risk group

All-cause mortality was reported for three trials in 339 evaluable participants.[105,121,167] One trial, in 27 participants was 24 weeks or longer.[167] This study compared pravastatin (40 mg/day) plus gemfibrozil (1200 mg/day) with pravastatin (40 mg/day) in participants with familial type II-b hyperlipoproteinemia or familial combined hyperlipidemia, and reported no deaths throughout the followup duration of 48 to 92 weeks. Across all three trials of 12-92 weeks duration (Appendix D), two trials on 297 evaluable participants had a total of three deaths (Table 15). These could be meta-analyzed without asymmetry evident (Figure 35).[105,121] A nonsignificant odds ratio of 0.39 (95% CI 0.05, 3.22) was observed. Neither trial report included a procedure to guarantee allocation concealment, and sensitivity analyses were not conducted.

Only one trial of 18 weeks duration permitted a comparison of lower dose rosuvastatin (5 to 10 mg/day) in combination with fenofibrate (67mg/day) with higher dose rosuvastatin (40 mg/day) as monotherapy in 166 evaluable participants (Table 15, Appendix D).[121] All participants on this trial had diabetes mellitus at baseline and required intensive lipid lowering therapy.[121] In this study, participants on combination therapy received fixed doses of medications and participants on monotherapy had their medication dose increased every 6 weeks if LDL-c cholesterol remained above 50 mg/dL. The estimable odds ratio (combination vs monotherapy) for this trial, based upon two deaths, was 0.46 (95% CI 0.03, 7.57).

Fatal myocardial infarction: fibrate-statin combination versus statin monotherapy

Two trials on 194 evaluable participants reported one fatal MI. One 52 week trial, in 48 participants, compared fluvastatin (80 mg/day) and fenofibrate (200 mg/day) with fluvastatin (80 mg/day) as monotherapy in participants with combined hyperlipidemia, type II diabetes mellitus and coronary heart disease. It reported no fatal myocardial infarction.[118] Another 12 week trial in 146 evaluable participants reported one fatal myocardial infarction, yielding an nonsignificant odds ratio for fatal myocardial infarction of 0.31 (95% CI 0.01, 7.77) based on a single death.[105] None of the trials comparing lower dose statin plus fibrate with higher dose of the same statin reported fatal myocardial infarction (Table 15, Appendix D).Myocardial infarction and acute coronary cyndrome: fibrate-statin combination versus statin monotherapy

A single trial with a followup of 52 weeks on 48 evaluable participants comparing fluvastatin (80 mg/day) and fenofibrate (200 mg/day) with fluvastatin (80 mg/day) as monotherapy in participants with combined hyperlipidemia, type II diabetes mellitus and coronary heart disease reported no occurances of myocardial infarction (including non-fatal myocardial infarction) or acute coronary syndrome (Appendix D).[118]

Serious Adverse Events: fibrate-statin combination versus statin monotherapy

Two trials on 651 evaluable participants reported the proportion of participants experiencing serious adverse events (Table 15, Appendix D).[115,118] Derosa et al,[118] in the 52 week trial described above, reported no serious adverse events in 48 participants requiring intensive lipid

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lowering therapy. Another trial of 12 weeks duration, comparing simvastatin (20 mg/day) and fenofibrate (200 mg/day) with simvastatin (20 mg/day) as monotherapy in 604 participants reported 17 serious adverse events and an odds ratio (combination vs monotherapy) of 1.2 (95% CI 0.42, 3.46) (Table 15, Appendix D).[115]

Non-randomized controlled trial evidence: fibrate-statin combination versus statin monotherapy

One multicenter, non-randomized controlled 36 week trial comparing fluvastatin (80mg/day) plus gemfibrozil (1200 mg/day) with fluvastatin (20, 40 and 80 mg/day) in a conditional dose titration reported 11 deaths in 1077 evaluable participants with or without CHD, with triglycerides < 400 mg/dL, and a mean LDL-c baseline of 186 mg/dL.[78] A single death was reported among 162 participants receiving combination therapy, while for monotherapy the deaths were 1/77 participants receiving fluvastatin 20mg/day, 4/237 receiving fluvastatin 40 mg/day, and 5/601 receiving fluvastain 80 mg/day. No other outcome of interest was reported (Table 16).

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Key Question 2: Do these regimens differ in reaching LDL-c targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

Overview of Included Studies

Eleven trials, none with crossover design, randomizing 1991 participants compared statin plus fibrate combinations with statin monotherapy and reported one or more surrogate efficacy or harms outcomes other than serious adverse events and cancer [Table study categorization].[41,105,115,118,121,129,142,143,167,171,174] Three trials provided information on participants' descent,[115,118,121] with 90-100% of participants of European descent, 2.8% of African descent, and 6.5% of Hispanic descent. Trial duration ranged from 6 to 104 weeks, with an average of 32 weeks. No trial was conducted exclusively in a particular gender, and on average 40% of participants were female (range 11 to 58%). The average of mean ages of participants was 57 years (range of mean age 49 to 60 years). Five trials recruited outpatients,[41,105,121,167,171] one trial recruited inpatients,[174] and five trials did not report recruitment setting. The mean Jadad score was 2 (range, 1 to 3) and two trials had adequate allocation concealment [115,142] Five trials recruited participants requiring intensive lipid lowering treatment, because of established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL.[118,121,129,143,174] These five trials randomized 598 participants.

Across trials, participants were of heterogeneous characteristics including those with familial combined hypercholesterolemia,[41,115,143,167,171] diabetes mellitus,[121,129,143] established vascular disease and/or CHD risk equivalent and/or diabetes mellitus,[118] and those reporting prior statin exposure.[115,118,129] There was one trial exclusively on participants with metabolic syndrome.[142] Most trials excluded participants with triglycerides above 300 to 600 mg/dL, patients with recent or unstable vascular disease, uncontrolled diabetes mellitus and hypertension, liver and muscle disease or high ALT, AST and CPK, and impaired renal function. No trial reported employing a fibrate plus statin combined pill.

Outcomes without Evidence

No randomized controlled trial yielded relevant data regarding the proportion of participants who adhered to treatment, carotid or coronary plaque area/volume, or a measure of stenosis and/or calcification. Data were synthesized for all remaining outcomes.

Surrogate Outcomes

Participants reaching LDL-c ATPIII targets: fibrate-statin combination versus statin monotherapy

Two trials on 240 evaluable participants reported 197 (82%) participants reaching the ATP III LDL-c targets. Both trials were conducted in participants requiring intensive lipid lowering therapy, with followup durations of 18 and 24 weeks (Table 17, Appendix D). No consistent trend was observed and significant heterogeneity prevented data being pooled (I^2 = 84%) (Figure 36). The 24 week trial, on 80 participants compared atorvastatin (20 mg/day) and fenofibrate (200 mg/day) with atorvastatin (20 mg/day) in participants with combined hyperlipidemia and type II diabetes mellitus, and had an estimable odds ratio of 9.75 (95% CI 1.16, 82.11) favoring

combination therapy.[143] In contrast, the 18 week trial comparing rosuvastatin (5-10 mg/day) plus fenofibrate (67mg/day) with rosuvastatin (40 mg/day) as monotherapy in 150 evaluable participants with diabetes mellitus, showed a nonsignificant odds ratio of 0.50 (0.20, 1.24).[121] Only the latter trial permitted a comparison of lower dose statin plus fenofibrate with higher dose monotherapy using the same statin, or provided data for this comparison on those requiring intensive lipid lowering therapy.[121] In this study participants on combination therapy received fixed doses of medications and participants on monotherapy had their medication dose increased every 6 weeks if LDL-c cholesterol remained above 50 mg/dL. All participants had diabetes mellitus at baseline.

LDL-c, post-treatment means or mean change scores: fibrate-statin combination versus statin monotherapy

Seven trials provided 8 pairs of analyzable data in 759 evaluable participants.[105,118,129,142,143,171,174] Followup duration ranged from 6 to 54 weeks, but most trials were less than 24 weeks duration. A significant pooled mean difference of -4.98 mg/dL (95% CI -9.06 mg/dL, -0.89 mg/dL) in favor of combination therapy was observed, and the results were not significantly heterogeneous (I^2 = 43%) (Figure 37). Across trials, participant characteristics were diverse and included those who were only of South Asian decent,[174] those with familial hypercholesterolemia,[143,171] and those with established CHD or risk equivalent.[118,129,174] All seven trials compared identical statins, and all but one used the same dose of statin in combination and monotherapy.[174] Asymmetry was not evident on the funnel plot (Figure 37).

Restricting the analysis to those requiring intensive lipid lowering therapy, 4 trials randomizing 419 participants yielded a nonsignificant pooled mean difference of -5.15 mg/dL (95% CI -10.77 mg/dL, 0.47 mg/dL) without significant heterogeneity (I^2 = 44%) (Table 18, Figure 38). [118,129,143,174] Participants in these trials had diabetes mellitus [118,129,143] and/or established vascular diseases,[118,174] and followup duration ranged from 12 to 52 weeks. Trials compared identical statins in combination and monotherapy, and one compared a lower dose of statin plus fibrate with higher dose monotherapy using the same statin.[174] In two of its four arms this trial compared lower dose simvastatin (20 mg/day) plus fenofibrate (200 mg/day) with higher dose simvastatin (40 mg/day) as monotherapy for 12 weeks in 45 evaluable South Asian participants, all with established coronary artery diseases prior to randomization.[174] No difference in means was observed – mean difference 0.00 mg/dL (95% CI -15.38 mg/dL, 15.38 mg/dL) (Appendix D).

LDL-c, percentage mean change from baseline: fibrate-statin combination versus statin monotherapy

Three trials of 12 to 18 weeks duration randomizing 904 evaluable participants yielded relevant data but because of high statistical heterogeneity (I^2 = 82%) data were not pooled (Figure 41).[115,121,129] One trial in a North America population, 90% of European descent, with prior use of statins showed a statistically significant difference in means of -5.4% (95% CI -8.39%, -2.41%) in favor of the statin plus fenofibrate combination.[115] Results were similar, but not statistically significant, in two trials exclusively in high risk participants with diabetes mellitus, with a pooled mean difference of 4.82% (95% CI -0.35%, 9.99%) (Figure 42).[121,129] Across the three trials, only one permitted comparison of lower dose rosuvastatin (10 mg/day) plus fenofibrate (67mg/day) with higher dose rosuvastatin (40 mg/day) monotherapy in 104

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evaluable participants.[121] A nonsignificant mean difference of 4.5% (95% CI -4.1%, 13.1%) was observed (Table 18).

HDL-c, post-treatment means or mean change scores: fibrate-statin combination versus statin monotherapy

Seven trials yielded 8 pairs of analyzable data in 759 evaluable participants. Due to high statistical heterogeneity (I^2 = 60%) data were not pooled (Figure 44).[105,118,129,142,143,171,174] All seven trials compared identical statins, and all but one used the same dose of statin in combination and monotherapy.[174] Followup ranged from 6 to 54 weeks, but most trials were less than 24 weeks in length. Six pairs of data showed differences in means ranging from 0 to 7.74 mg/dL in favor of statin plus fibrate combinations (Figure 44, Appendix D). No difference in means was observed in the other two trials, one exclusively in participants with diabetes mellitus,[129] and the other exclusively in participants with coronary artery disease.[174] Asymmetry was not evident on the funnel plot (Figure 44).

Similarly, inconsistent results are observed in the four trials comparing combination therapy with monotherapy in participants requiring intensive lipid lowering therapy. Mean differences ranged from 0 to 7 mg/dL (Table 19, Appendix D). Participants in these trials had diabetes mellitus [118,129,143] and/or established vascular diseases,[118,174] and followup ranged from 12 to 52 weeks. One trial allowed comparison in two of its four arms, fixed lower dose simvastatin (20 mg/day) plus fenofibrate (200 mg/day) with higher dose simvastatin (40 mg/day) monotherapy for 12 weeks in 45 evaluable South Asian participants, all with established coronary artery diseases prior to randomization.[174] The mean difference was 0.00 mg/dL (95% CI 7.58 mg/dL, 7.58 mg/dL) (Table 19).

HDL-c, percentage mean change from baseline: fibrate-statin combination versus statin monotherapy

Three trials with followup duration of 12 to 18 weeks in 964 evaluable participants reported statistically significant mean difference of 7.44% (95% CI 4.95%, 9.92%) (Figure 45) favoring the statin plus fenofibrate combination.[115,121,129] Two trials were exclusively in participants with diabetes mellitus,[121,129] and two were in participants with prior use of statins.[115,129] All three trials compared identical statins in combination and monotherapy, and all but one [121] investigated simvastatin (20 mg/day). Doses of fenofibrate varied from 67 to 200 mg/day. Pooled mean differences for the two trials conducted in participants requiring intensive lipid lowering therapy were 5.18% (95% CI 1.23%, 9.11%) (Table 19).[121,129] One trial permitted comparison of lower dose statin in combination with higher dose monotherapy with the same statin.[121] In the trials in participants with diabetes mellitus, fixed dose treatment with rosuvastatin 10 mg/day plus fenofibrate (67 mg/day) was compared with conditionally dosed rosuvastatin up to 40 mg/day, over 18 weeks. LDL-c mean percentage difference between treatments was 4.81% (95% CI -0.56%, 10.18%) (Table 19).

TC:HDL-c ratio, post-treatment means or mean change scores: fibrate-statin combination versus statin monotherapy

Two 12 week trials yielded three pairs of data in 217 evaluable participants, but because of high statistical heterogeneity (I^2 = 86%) data were not pooled.[105,174] No consistent trend was observed, and the difference in means varied from 0% to -8.9% (Appendix D). Trials compared identical statins, one trial was exclusively in inpatients with diagnosed coronary artery

diseases,[174] while in the other trial participants were outpatients of mixed risk.[105] One trial compared in two of its four arms fixed dose simvastatin (20 mg/day) plus fenofibrate (200mg/day) with simvastatin (40 mg/day) monotherapy, over a 12 week period. No difference in means between treatments was observed, (DM 0.00; 95% CI -1.04 mg/dL, 1.04 mg/dL) (Table 20, Appendix D).[174]

Data associated with 91 participants, all with established vascular diseases and requiring intensive lipid lowering was provided for the same trial mentioned above.[174] A nonsignificant mean difference of -0.22 mg/dL (95% CI -0.73 mg/dL, 0.29 mg/dL) was observed (Table 20).

TC:HDL-c ratio, percentage mean change from baseline: fibrate-statin combination versus statin monotherapy

A single trial on participants requiring intensive lipid lowering therapy because of diabetes mellitus compared fixed lower dose rosuvastatin (10 mg/day) in combination with fenofibrate (67mg/day) with conditionally dosed rosuvastatin up to 40 mg/day monotherapy, in 104 evaluable participants. The nonsignificant mean difference was -2.7% (95% CI -10.46%, 5.06%) (Table 20).[121]

Measures of Adherence and Harm

Participants with at least one adverse event: fibrate-statin combination versus statin monotherapy

Three trials of 12 to 52 weeks duration in 362 evaluable participants reported 90 adverse events, but because of high statistical heterogeneity (I^2 = 60%) data were not pooled (Table 21, Appendix D). No consistent trend was observed. One 52 week trial compared fluvastatin (80 mg/day) plus fenofibrate (200 mg/day) with fluvastatin (80 mg/day) in 48 evaluable participants of European descent with established coronary artery diseases and prior use of statins. The authors reported an estimable odds ratio of 1.43 (95% CI 0.22, 9.44) favoring monotherapy based on 5 events.[118] A second trial on 168 participants with followup duration of 18 weeks, comparing rosuvastatin (5 to 10 mg/day) plus fenofibrate (67mg/day) with rosuvastatin (40 mg/day) monotherapy in participants with diabetes mellitus, yielded an odds ratio of 0.73 (0.34, 1.57) favouring monotherapy based on 38 events.[121] A third 12 week trial comparing pravastatin (40 mg/day) and gemfibrozil (1200 mg/day) with pravastatin (40 mg/day) in 146 evaluable participants yielded a significant odds ratio of 2.42 (95% CI 1.18, 4.99) favoring monotherapy based on 47 events (Appendix D).[105] Only one of the described trials compared lower dose statin plus fenofibrate with higher dose monotherapy (results as above).[121]

Participants withdrawing due to adverse event: fibrate-statin combination versus statin monotherapy

Five trials of 12 to 52 weeks duration and 1269 evaluable participants reported 41 withdrawals due to adverse events, but because of high statistical heterogeneity (I^2 = 56%) data were not pooled (Table 21, Appendix D). No consistent trend was observed and estimable odds ratios ranged from 0.29 to 7.22 (Appendix D). One 24 week trial reported no withdrawal due to an adverse event.[143] Two trials were conducted exclusively in participants with diabetes mellitus,[121,143] and three in participants with familial combined hyperlipidemia.[41,115,143] All but one trial [41] compared identical statins in combination and monotherapy, and one trial employed the highest label doses of statins as monotherapy.[121]

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Participants with AST and/or ALT above 3 times the upper limit of normal, and/or hepatitis: fibrate-statin combination versus statin monotherapy

In four trials of 18 to 54 weeks, in 841 evaluable participants, 11 cases of elevated AST/ALT above three times the upper limit were reported (Table 21, Appendix D).[41,121,142,143] One trial, in 80 participants, compared atorvastatin (20 mg/day) and fenofibrate (200 mg/day) with atorvastatin (20 mg/day) in participants with combined hyperlipidemia and diabetes mellitus, and no participants had any element of the composite outcome during 24 weeks of followup.[143] Three trials of 18 to 54 weeks, in 761 evaluable participants, could be meta-analyzed and showed a pooled odds ratio of 2.38 (95% CI 0.41, 14.0) favoring monotherapy based on 11 events (Table 21, Appendix D).[41,121,142] In a single trial in 168 evaluable participants comparing rosuvastatin plus fibrate with higher dose rosuvastatin monotherapy, six participants in the combination therapy experienced AST/ALT above three times the upper limit of normal, yielding an estimable odds ratio of 6.35 (95% CI 0.35, 114.85) favoring monotherapy (Table 21).

Participants with myalgia: fibrate-statin combination versus statin monotherapy

In six trials of 12 to 104 weeks, 32 cases of myalgia were reported in 1439 evaluable participants (Table 21, Appendix D). One trial comparing atorvastatin (20 mg/day) plus fenofibrate (200 mg/day) with atorvastatin (10 mg/day) in two of its four arms, reported no cases of myalgia among participants during 12 weeks followup.[174] Data on 1389 evaluable participants could be meta-analyzed without evident heterogeneity (Table 21).[41,105,115,121,167,174] A nonsignificant odds ratio of 1.17 (95% CI 0.52, 2.62) was observed, and asymmetry was not evident on the funnel plot (Figure 46). Two trials using different statins permitted a comparison of lower dose statin plus fenofibrate with higher dose monotherapy using the same statin.[121,174] One trial compared conditionally dosed rosuvastatin (5-10 mg/day) plus fenofibrate (67mg/day) with a fixed higher dose of rosuvastatin (40 mg/day) monotherapy in 168 evaluable participants with diabetes mellitus, yielding an estimable odds ratio of 1.39 (0.14, 13.71) based on four cases of myalgia (Table 21) [121] Another trial compared lower dose simvastin (20 mg/day) plus fenofibrate (200 mg/day) with higher dose simvastin (40 mg/day) monotherapy in 50 evaluable participants of South Asian descent, yielding an estimable odds ratio of 0.18 (95% CI 0.01, 4.04) based on two cases of myalgia (Table 21).[174]

Participants with CPK above 10 times the upper limit of normal: fibrate-statin combination versus statin monotherapy

Five trials in 1199 evaluable participants reported one event of CPK above 10 times the upper limit (Table 21). Four trials reported no events in participants during a followup of 12-24 weeks.[105,121,129,143] One trial of 12 weeks duration on 605 evaluable participants reported one event of elevated CPK and an estimable odds ratio of 1.51 (95% CI 0.06, 37.22) (Table 21, Appendix D).[115] Lower dose rosuvastatin plus fibrate was compared with higher dose monotherapy in one trial with no events.[121]

Participants with rhabdomyolysis: fibrate-statin combination versus statin monotherapy

Three trials in 951 evaluable participants reported no events of rhabdomyolysis during a followup of 12 weeks (Table 21, Appendix D).[105,115,129]

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Key Question 3: Compared with higher-dose statins, and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

Subgroups without randomized controlled trial evidence: fibrate-statin combination versus statin monotherapy

No randomized controlled trial reported relevant data on participants in the following subgroups: those with LDL-c above 190 mg/dL, with cerebrovascular diseases, of African descent, of Asian descent or of Hispanic descent.

Longer term outcomes

All-cause mortality or vascular death: fibrate-statin combination versus statin monotherapy

Participants with diabetes mellitus. One trial with estimable data on all-cause mortality permitted the comparison of lower dose rosuvastatin (5-10 mg/day) plus fenofibrate (67 mg/day) with higher dose rosuvastatin (40 mg/day) monotherapy in 166 evaluable participants with diabetes mellitus.[121] Those on combination therapy received fixed doses of medications, while participants on monotherapy had their medication dose increased every 6 weeks if LDL-c cholesterol remained above 50 mg/dL. A nonsignificant odds ratio of 0.46 (95% CI 0.03, 7.57) was observed (Table 15). No studies reported data on vascular death for participants with diabetes mellitus.

Surrogate outcomes

Participants attaining LDL-c ATPIII targets: fibrate-statin combination versus statin monotherapy

Participants with diabetes mellitus. Two trials of 18 to 24 weeks, in 240 evaluable participants reported 197 participants reaching ATP III LDL-c targets (Table 17). No consistent trend was observed and significant heterogeneity prevented data to be pooled (I^2 = 84%) (Figure 36). The 24 week trial in 80 participants compared atorvastatin (20 mg/day) plus fenofibrate (200 mg/day) with atorvastatin (20 mg/day) in participants with combined hyperlipidemia and type II diabetes mellitus, yielding an estimable odds ratio of 9.75 (95% CI 1.16, 82.11) favoring the combination therapy.[143] In contrast, a 18 week trial comparing rosuvastatin (5-10 mg/day) plus fenofibrate (67mg/day) with rosuvastatin (40 mg/day) monotherapy in 160 evaluable participants with diabetes mellitus, showed a nonsignificant odds ratio of 0.50 (95% CI 0.20, 1.24) (forest plot).[121] The latter trial compared lower dose rosuvastatin plus fenofibrate with higher dose rosuvastatin monotherapy (Table 17).[121]

LDL-c, post-treatment means or mean change scores: fibrate-statin combination versus statin monotherapy

Participants with diabetes mellitus. Three trials in 328 evaluable participants were significantly heterogeneous (I^2 = 55%) (Figure 39).[118,129,143] No consistent trend was observed during 12 to 52 weeks followup. One 12 week trial [129] yielded a mean difference of 0.00 mg/dL (95% CI -8.55 mg/dL, 8.55 mg/dL), and two trials of more than 24 weeks yielded mean differences in favor of combination therapy of -8 mg/dL (95% CI -10.9 mg/dL, -5.14 mg/dL) and -15 mg/dL (95% CI -27.8 mg/dL, -2.24 mg/dL) respectively.[118,143] None of the trials compared lower dose statin plus fibrate with higher dose statin monotherapy.

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Participants with established vascular disease. Two trials of 12 to 52 weeks , in 139 evaluable participants reported a nonsignificant pooled mean difference of -5.43 mg/dL (95% CI -13.86 mg/dL, 3.00 mg/dL) (Figure 40).[118,174] One trial compared, in two of its four arms, fixed lower dose simvastatin (20 mg/day) plus fenofibrate (200 mg/day) with higher dose simvastatin (40 mg/day) monotherapy, for 12 weeks in 45 evaluable South Asian participants.[174] The mean difference was 0 mg/dL (95% CI -15.38 mg/dL, 15.38 mg/dL) (Table 18).

LDL-c, percentage mean change from baseline: fibrate-statin combination versus statin monotherapy

Participants with diabetes mellitus. Two trials of 12 to 18 weeks, in 304 evaluable participants yielded a pooled mean difference of 4.82% (95% CI -0.35%, 9.99%) (Figure 43, Table 18) .[121,129] One trial compared lower dose rosuvastatin plus fenofibrate with higher dose rosuvastatin monotherapy, yielding a nonsignificant mean difference of 4.5% (95% CI -4.10%, 13.10%) (Figure 43, Table 18)[121]

HDL- c, post-treatment means or mean change scores: fibrate-statin combination versus statin monotherapy

Participants with diabetes mellitus. Three trials yielded data on 328 evaluable participants, but no pooled results are presented because of significant heterogeneity (I^2 = 83%) (Table 19).[118,129,143] No consistent trend was observed during 12 to 52 weeks followup. One study [129] reported a nonsignificant mean difference of 0.7 mg/dL (95% CI -1.93 mg/dL, 3.33 mg/dL), and the two longer-term studies showed significant mean differences in favor of combination therapy of 5.3 mg/dL (95% CI 3.37 mg/dL, 7.23 mg/dL) and 7 (95% CI 4.08 mg/dL, 9.91 mg/dL) respectively [118,143] None of the trials compared lower dose statin plus fibrate with higher dose statin monotherapy.

Participants with established vascular diseases. Two trials of 12 to 52 weeks in 139 evaluable participants yielded a significant pooled mean difference of 5.43 mg/dL (95% CI 2.14 mg/dL, 8.73 mg/dL) in favor of combination therapy.[118,174] One 12 week trial comparing lower dose simvastatin plus fenofibrate with higher dose simvastatin monotherapy yielded a mean difference of 0.00 mg/dL (95% CI -15.38 mg/dL, 15.38 mg/dL) (Table 19).[174]

HDL-c, percentage mean change from baseline: fibrate-statin combination versus statin monotherapy

Participants with diabetes mellitus. Two trials of 12 to 18 weeks in 364 evaluable participants yielded a significant pooled mean difference of 5.17% (95% CI 1.23%, 9.11%) (Table 19).[121,129] One trial compared lower dose rosuvastatin plus fenofibrate with higher dose rosuvastatin monotherapy, yielding a nonsignificant mean difference of 4.81% (95% CI -0.56%, 10.18%) (Table 19).[121]

TC:HDL-c ratio, post-treatment means or mean change scores: fibrate-statin combination versus statin monotherapy

Participants with diabetes mellitus. One 12 week trial in 91 evaluable participants permitted 2 comparisons among four treatment arms, yielding a pooled mean difference of -0.22 (95% CI -0.73, 0.28).[174] Two of its four arms allowed comparison of fixed lower dose simvastatin plus fenofibrate with higher dose simvastatin monotherapy in 45 evaluable South Asian participants, yielding a mean difference of 0.00 (95% CI -1.04, 1.04) (Table 20).

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TC:HDL-c ratio, percentage mean change from baseline: fenofibrate-statin combination versus statin monotherapy

Participants with diabetes mellitus. One trial comparing lower dose rosuvastatin (10 mg/day) plus fenofibrate (67mg/day) with higher dose rosuvastatin (40 mg/day) monotherapy in 104 evaluable participants yielded a nonsignificant mean difference of -2.7 (95% CI -10.46, 5.06) (Table20).[121]

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Tables and Figures: Fibrate - Statin Combination Therapy versus Statin Monotherapy

Table 15: Quantitative syntheses of longer-term outcomes data (clinical, serious adverse events and cancer) for fibrate plus statin combination therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant intervention groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
All-cause mortality						
All trials[105,121,167]	3	339	3	0.39	0.05	3.22
Rosuvastatin Lower dose statin in combination therapy versus higher dose monotherapy[121] Participants requiring intensive lipid lowering therapy, due to diabetes mellitus[121]	1	166	2	0.46	0.03	7.57
Fatal Myocardial Infarction						
All trials[105,118]	2	194	1	0.31	0.01	7.77
Myocardial Infarction						
Non-fatal myocardial infarction[118]	1	48	0			
Any myocardial infarction[118]	1	48	0			
Acute coronary syndrome						
All trials[118]	1	48	0			
Serious Adverse Event(s)						
All trials[38,115]	2	651	17	1.20	0.42	3.46

Abbreviations: CI 95% confidence interval

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Table 16. Summary of non-randomized evidence on fluvastatin plus gemfibrozil

Trial	Design Duration Downs and Black score	Patients (LDL-c mg/dL)	Monotherapy Dose (mg/day)	Combination Therapy Dose (mg/day)	Results	Limitations	Applicability	Conclusion
van Dam (2001) [78] Multicenter / Europe Pharmaceutical Industry	CCT Conditional dose titration and fibrate addition to statin therapy over 9 months Stable doses for 1 year 15/28	1501 (N evaluable = 1077) outpatients with or without CHD TG < 400 mg/dL Mean baseline LDL-c = 186 mg/dL	Fluvastatin (20, 40 and 80 mg)	Fluvastatin plus (80); Gemfibrozil (1200)	All-cause mortality: F20 = 1/77 F40 = 4/237 F80 = 5/601 F80+G1200 = 1/162 Mortality and other clinical outcomes of interest, SAE and cancer not reported	Unlike statin monotherapy groups, patients on combination therapy had combined hyperlipidemia (additional hypertriglyceridemia). Those on statin monotherapies differed in LDL-c target goals and degree of dysplipidemia. Study was not powered for the outcome of mortality	Narrow eligibility criteria, lack of reporting of important clinical outcomes, 1 year stable dose follow-up, and low event rates are suggestive of low applicability	Results are inconclusive given low event rate and lack of statistical significance

Abbreviations: CCT = clinical controlled trial, F = fluvastatin, G = gemfibrozil, LDL-c = low density lipoprotein cholesterol, N = number, SAE = serious adverse events, TG = triglycerides

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Table 17. Quantitative syntheses of participants attaining ATP III LDL-c targets data, for fibrate plus statin combination therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Relative probability of attaining ATPIII LDL-c goal						
All trials						
All participants with diabetes mellitus	2	240	197	-	-	-
Participants requiring intensive lipid lowering therapy [121,143]						
Rosuvastatin						
Lower dose statin in combination therapy versus higher dose monotherapy[121,143]	1	160	126	0.50	0.20	1.24
Participants with diabetes mellitus [121,143]	1	160	126	0.50	0.20	1.24

Abbreviations: ATP III = the third Adult Treatment Panel III Adult Treatment Panel of the National Cholesterol Education Program, CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

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Table 18. Quantitative syntheses of LDL-c data for fibrate plus statin combination therapy compared with statin monotherapy

	Number of trials	Number of participants in relevant treatment groups	Point Estimate	Lower CI	Upper CI
Difference in mean LDL-c post-treatment / change score from baseline (mg/dL)					
All trials [105,118,129,142,143,171,174]	7	759	-4.98	-9.06	-0.89
Simvastatin					
Lower dose statin in combination therapy versus higher dose monotherapy [174]	1	45	0.00	-15.38	15.38
Participants in need of intensive lipid lowering therapy – trials of 24 weeks or more [118,143]	2	128	-8.63	-12.54	-4.71
Participants in need of intensive lipid lowering therapy – trials of less than 24 weeks [129,174]	2	291	-6.3	-9.69	-2.91
Participants in need of intensive lipid lowering therapy – all trials [118,129,143,174]	4	419	-5.15	-10.77	0.47
Participants with diabetes mellitus [118,129,143]	*3*	328	-	-	-
Participants with established vascular disease – trials of 24 weeks or more [118]	1	48	-15	-27.76	-2.24
Participants with established vascular disease – all trials [118,174]	2	139	-5.43	-13.86	3.00
Participants with established vascular disease – trials of less than 24 weeks [174]	1	91	1.99	-9.25	13.22
Difference in mean LDL-c percentage change from baseline (%)					
All trials [115,121,129]	3	904	-	-	-
Lower dose statin in combination versus higher dose monotherapy [121]	1	104	4.50	-4.10	13.10
Participants in need of intensive lipid lowering therapy, all with diabetes mellitus [121,129]	2	304	4.82	-0.35	9.99

AbbreviationsCI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

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Table 19. Quantitative syntheses of HDL-c data, for fibrate plus statin combination therapy compared with statin monotherapy

	Number of trials	Number of participants in relevant treatment groups	Point Estimate	Lower CI	Upper CI
Difference in mean HDL-c post-treatment / change score from baseline (mg/dl)					
All trials [105,118,129,142,143,171,174,174]	7	759	-	-	-
Simvastatin					
Lower dose statin in combination therapy versus higher dose monotherapy [174]	1	45	0.00	-7.58	7.58
Participants requiring intensive lipid lowering therapy, all with established vascular diseases [174]					
Participants requiring intensive lipid lowering therapy [118,129,143,174]	4	419	-	-	-
Participants with diabetes mellitus [118,129,143]	3	328	-	-	-
Participants with vascular disease [118,174]	2	139	5.43	2.14	8.73
Difference in mean HDL-c percentage change from baseline (%)					
All trials [115,121,129]	3	964	7.44	4.95	9.92
Rosuvastatin					
Lower dose statin in combination therapy versus higher dose monotherapy	1	164	4.81	-0.56	10.18
Participants requiring intensive lipid lowering therapy, all with diabetes mellitus [121]					
Participants in need of intensive lipid lowering therapy , all with diabetes mellitus [121,129]	2	364	5.18	1.23	9.12

Abbreviations: CI = 95% confidence interval, HDL-c = high density lipoprotein cholesterol

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Table 20. Quantitative syntheses of total cholesterol:HDL-c ratio data, for fibrate plus statin combination therapy compared with statin monotherapy

	Number of trials	Number of participants in relevant treatment groups	Point Estimate	Lower CI	Upper CI
Difference in mean TC:HDL-c post-treatment / change score from baseline					
All trials [105,174]	2	217	-	-	-
Simvastatin					
Lower dose statin in combination therapy versus higher dose monotherapy [174]	1	43	0.00	-1.04	1.04
Participants in need of intensive lipid lowering therapy					
All participants with established vascular diseases [174]	1	91	-0.22	-0.73	0.29
Difference in mean TC:HDL-c percentage change from baseline (%)					
All trials					
Rosuvastatin					
Lower dose statin in combination therapy versus higher dose monotherapy [121]	1	104	-2.70	-10.46	5.06
All participants with diabetes mellitus					
Participants in need of intensive lipid lowering therapy [121]					

Abbreviations: CI = 95% confidence interval, HDL-c = high density lipoprotein cholesterol, TC = total cholesterol

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Table 21. Quantitative syntheses of short-term harms and treatment adherence data for fibrate plus statin combination therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Participants with adverse events						
All trials [105,118,121]	3	362	90	-	-	-
Rosuvastatin Lower dose statin in combination therapy versus higher dose monotherapy [121]	1	168	38	0.73	0.34	1.57
Withdrawals due to adverse events						
All trials [41,105,115,121,143]	5	1269	41	-	-	-
Rosuvastatin Lower dose statin in combination therapy versus higher dose monotherapy [121]	1	168	5	0.29	0.05	1.82
AST and/or ALT ≥ 3 times the upper limit of normal, and/or hepatitis						
All trials[41,121,142,143]	4	841	11	2.38	0.41	14.00
Rosuvastatin Lower dose statin in combination therapy versus higher dose monotherapy[121]	1	168	6	6.35	0.35	114.85
Myalgia						
All trials [41,105,115,121,167,174]	6	1439	31	1.17	0.52	2.62
Rosuvastatin Lower dose statin in combination therapy versus higher dose monotherapy [121]	1	168	4	1.39	0.14	13.71
Simvastatin Lower dose statin in combination therapy versus higher dose monotherapy[174]	1	50	2	0.18	0.01	4.04
CPK ≥ 10 times the upper limit of normal						
All trials[105,115,121,129,143]	5	1199	1	1.51	0.06	37.22
Rosuvastatin Lower dose statin in combination therapy versus higher dose monotherapy [121]	1	168	0	-	-	-
Rhabdomyolysis (investigator defined)						
All trials[105,115,129]	3	951	0	-	-	-

Abbreviations: ALT = alanine transaminase, AST = aspartate transaminase, CI = 95% confidence interval, CPK = creatine phosphokinase

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Figure 35. Forest plot of all-cause mortality for fibrate plus statin therapy compared with statin monotherapy, in all participants

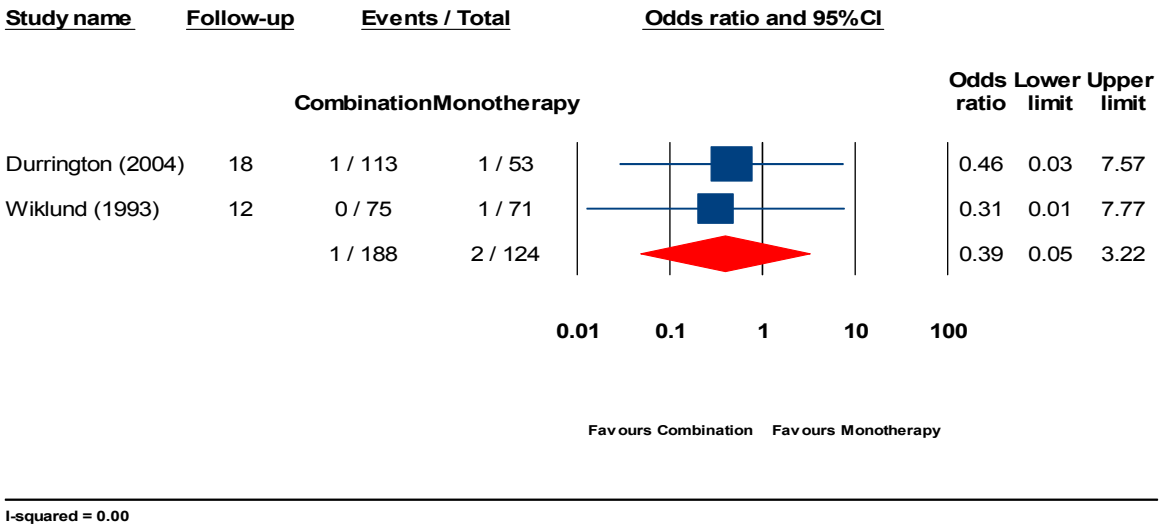


Figure 36. Forest plot of achievement of ATP III LDL-c targets, for fibrate plus statin therapy compared with statin monotherapy, in all participants, who required intensive lipid lowering therapy due to diabetes mellitus

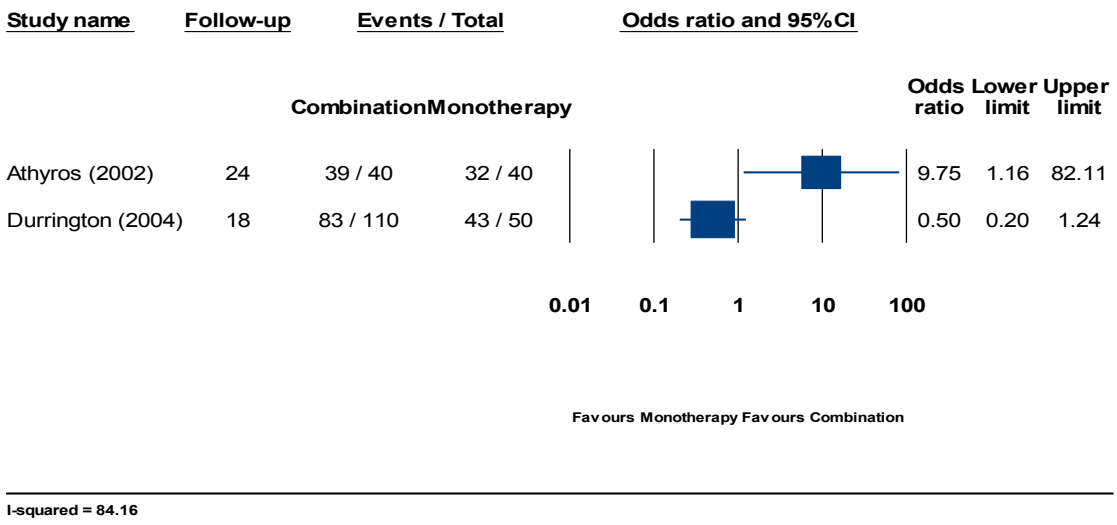
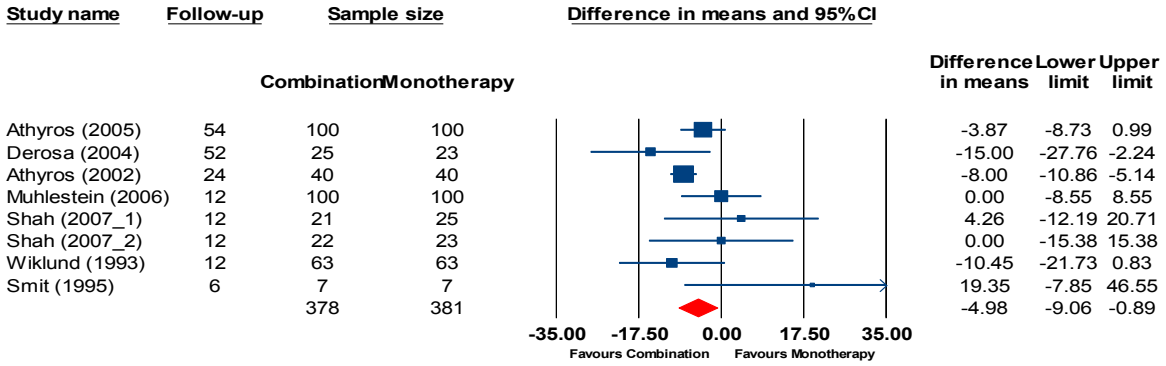


Figure 37. Forest and funnel plots of LDL-c, post-treatment means / mean change scores for fibrate plus statin therapy compared with statin monotherapy, in all participants



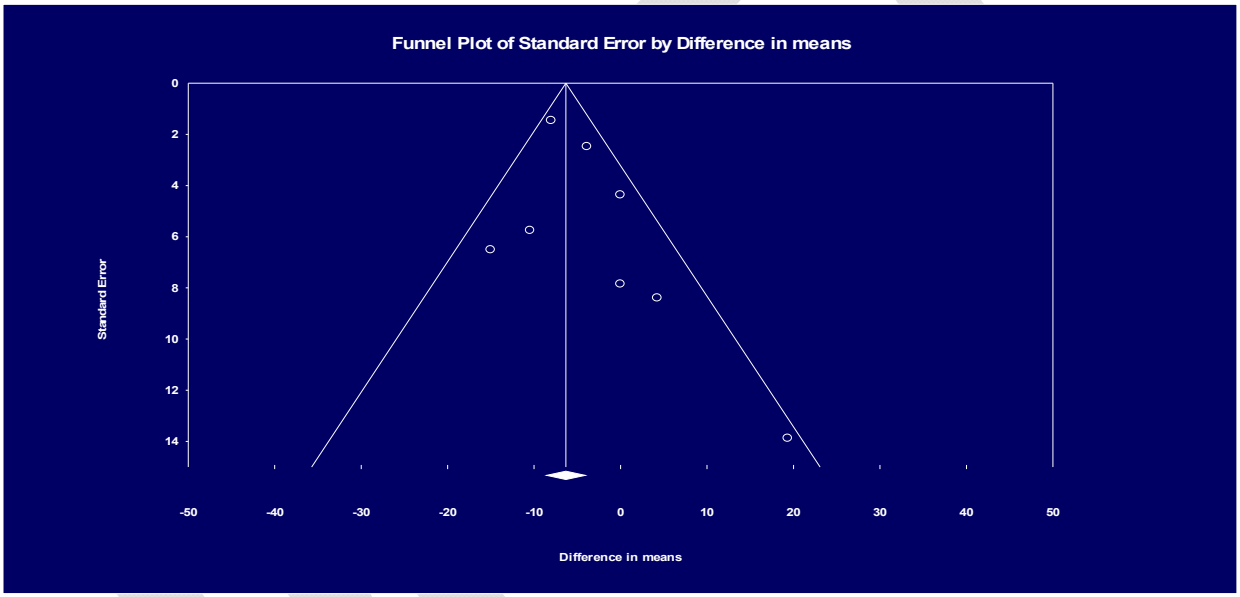
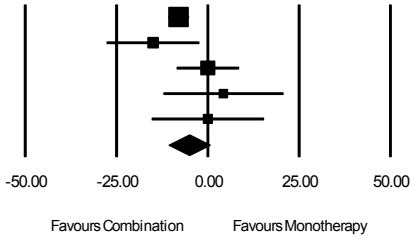


Figure 38. Forest plot of difference in LDL-c post-treatment means / mean change scores for fibrate plus statin therapy compared with statin monotherapy, in participants requiring intensive lipid lowering therapy

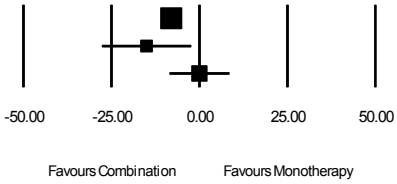
Followup	Study name	Statistics for each study: Difference in means	Standard error	Lower limit	Upper limit	Sample size: Combination	Monotherapy
24	Athyros (2002)	-8.00	1.46	-10.86	-5.14	40	40
52	Derosa (2004)	-15.00	6.51	-27.76	-2.24	25	23
12	Muhlestein (2006)	0.00	4.36	-8.55	8.55	100	100
12	Shah (2007_1)	4.26	8.39	-12.19	20.71	21	25
12	Shah (2007_2)	0.00	7.85	-15.38	15.38	22	23
		-5.15	2.87	-10.77	0.47		



Model: random effects I-squared = 44%

Figure 39. Forest plot of difference in LDL-c post-treatment means / mean change scores for fibrate plus statin therapy compared with statin monotherapy, in participants with diabetes mellitus

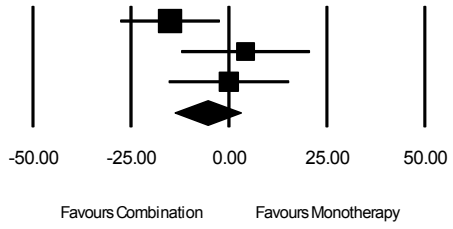
Followup	Study name	Statistics for each study: Difference in means	Standard error	Lower limit	Upper limit	Sample size: Combination	Monotherapy
24	Athyros (2002)	-8.00	1.46	-10.86	-5.14	40	40
52	Derosa (2004)	-15.00	6.51	-27.76	-2.24	25	23
12	Muhlestein (2006)	0.00	4.36	-8.55	8.55	100	100



Model: random effects I-squared = 54.5%

Figure 40. Forest plot of difference in LDL-c post-treatment means / mean change scores for fibrate plus statin therapy compared with statin monotherapy, in participants with established vascular diseases

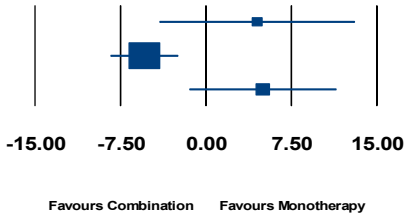
Followup	Study name	Statistics for each study				Sample size	
		Difference in means	Standard error	Lower limit	Upper limit	Combination	Monotherapy
52	Derosa (2004)	-15.00	6.51	-27.76	-2.24	25	23
12	Shah (2007_1)	4.26	8.39	-12.19	20.71	21	25
12	Shah (2007_2)	0.00	7.85	-15.38	15.38	22	23
		-5.43	4.30	-13.86	3.00		



Model: random effects I-squared = 49.7%

Figure 41. Forest plot of difference in LDL-c mean percentage change from baseline for fibrate plus statin therapy compared with statin monotherapy, in all participants

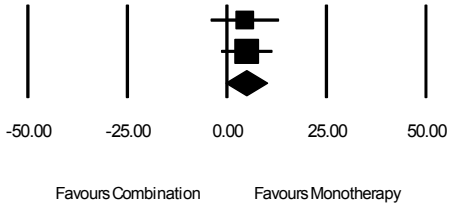
Study name	Follow-up	Sample size		Difference in means	Lower limit	Upper limit
		Combination	Monotherapy			
Durrington (2004)	18	53	51	4.50	-4.10	13.10
Grundy (2005)	12	399	201	-5.40	-8.39	-2.41
Muhlestein (2006)	12	100	100	5.00	-1.47	11.47



I-squared = 82.22

Figure 42. Forest plot of difference in LDL-c mean percentage change from baseline for fibrate plus statin therapy compared with statin monotherapy, in participants requiring intensive lipid lowering therapy

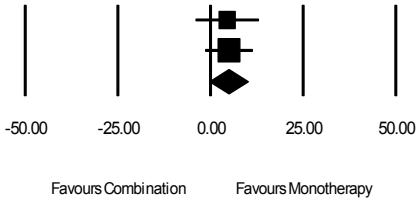
Followup	Study name	Statistics for each study				Sample size	
		Difference in means	Standard error	Lower limit	Upper limit	Combination	Monotherapy
18	Durrington (2004)	4.500	4.386	-4.096	13.096	53	51
12	Muhlestein (2006)	5.000	3.301	-1.470	11.470	100	100
		4.819	2.637	-0.350	9.989		



Model: random effects I-squared = 0%

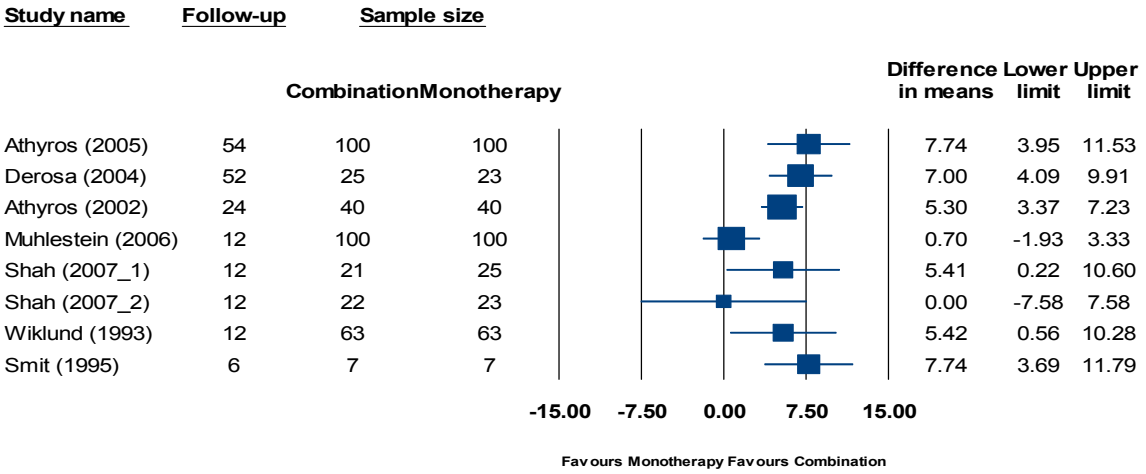
Figure 43. Forest plot of difference in LDL-c mean percentage change from baseline for fibrate plus statin therapy compared with statin monotherapy, in participants with diabetes mellitus

Followup	Study name	Statistics for each study				Sample size	
		Difference in means	Standard error	Lower limit	Upper limit	Combination	Monotherapy
18	Durrington (2004)	4.500	4.386	-4.096	13.096	53	51
12	Muhlestein (2006)	5.000	3.301	-1.470	11.470	100	100
		4.819	2.637	-0.350	9.989		



Model: random effects I-squared = 0%

Figure 44. Forest and funnel plots of difference in HDL-c post-treatment means / mean change scores for fibrate plus statin therapy compared with statin monotherapy, in all participants



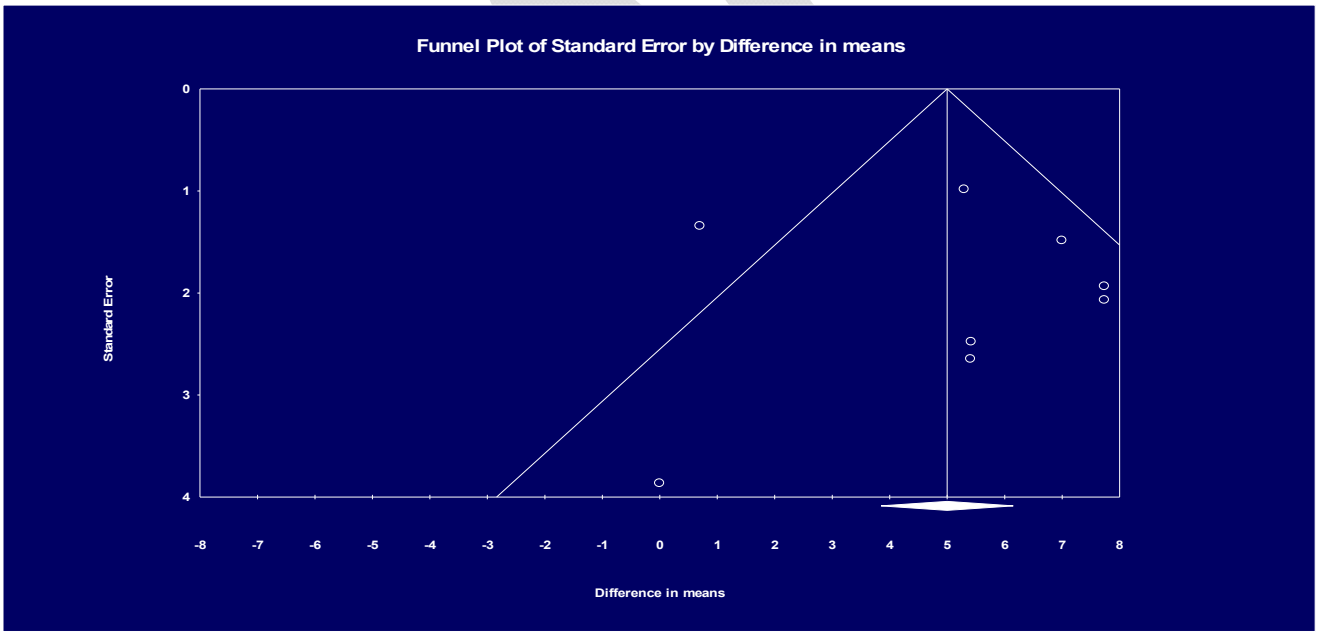
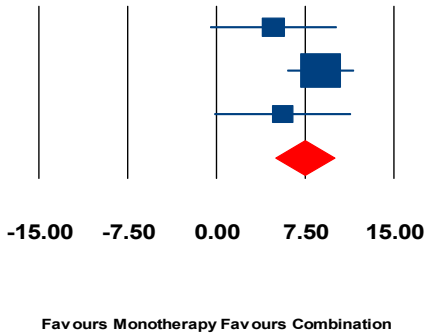


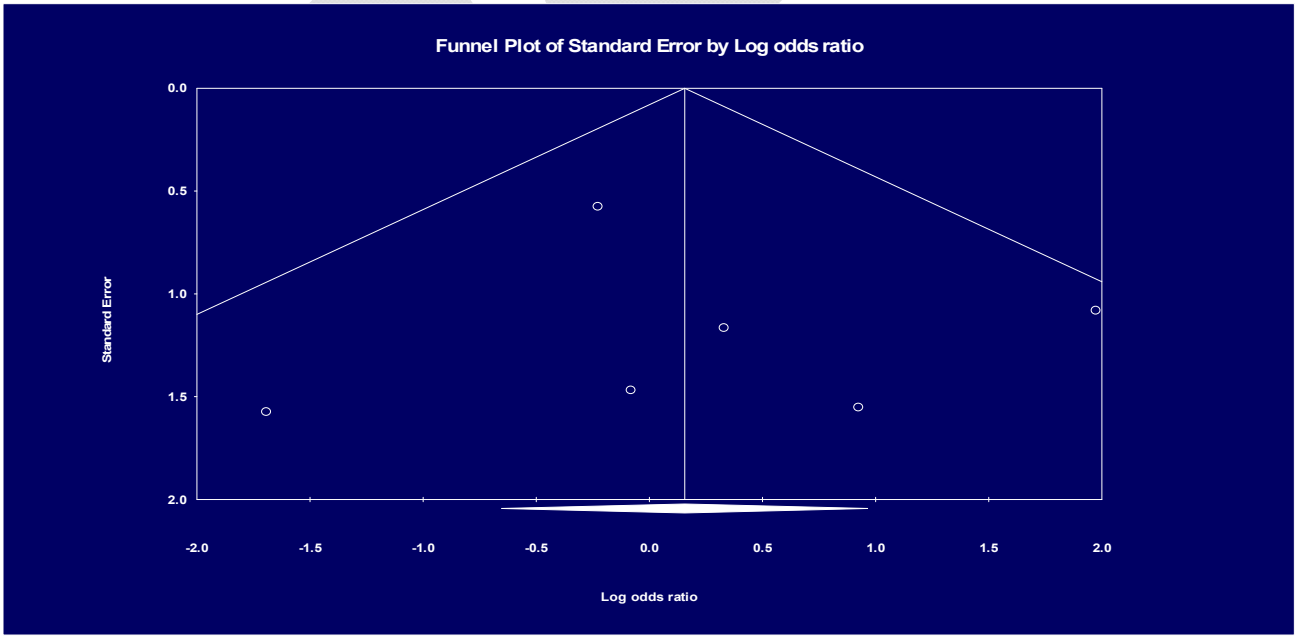
Figure 45. Forest and funnel plots of difference in HDL-c mean percentage change from baseline for fibrate plus statin therapy compared with statin monotherapy, in all participants

Study name	Follow-up	Sample size		Difference in means	Lower limit	Upper limit
		Combination	Monotherapy			
Durrington (2004)	18	113	51	4.81	-0.56	10.18
Grundy (2005)	12	399	201	8.80	5.96	11.64
Muhlestein (2006)	12	100	100	5.60	-0.19	11.39
		612	352	7.44	4.95	9.92



I-squared = 8.07

Figure 46. Funnel plot of incidence of participants with myalgia, for fibrate plus statin therapy compared with statin monotherapy, in all participants



Niacin-statin Combination Therapy versus Statin Monotherapy

Overview of included studies

A total of 13 randomized controlled trials evaluated relative efficacy and/or harms of the combination of a statin plus niacin compared with statin monotherapy, in a total of 1991 participants (Table 4, Appendix D). None of the included non-randomized studies addressed this particular comparison. Nine of the thirteen randomized trials had more than one associated journal published or FDA report (Table 6). The data reported in the two FDA reports[95,96] are similar to data presented in two published manuscripts.[133,162] The similarities included the inclusion/exclusion criteria, number of patients randomized and outcomes. However, since no direct connection could be found in the reports to confirm that they are the same trial, they were included as separate trial reports.

Eight trials were conducted in multiple centers,[40,95,96,122,133,138,151,162] and five in a single centre.[163,164,168,175,176] There were no trials exclusively in females, or participants of Asian, Hispanic, and/or African descent.

Reporting of participants' ethnic background was as follows:

- European descent: 8 trials, Mean = 87% (range, 82%-94%)
- Asian descent: 3 trials, Mean = 3% (range, 2%-4%)
- Hispanic descent: 4 trial, Mean = 3% (range, 0%-6%)
- African descent: 4 trial, Mean = 9% (range, 5%-15%)

Nine of thirteen trials were partially or completely sponsored by the pharmaceutical industry,[40,122,133,138,151,162-164,176] while this was not reported or unclear for three trials.[95,96,168]

Total Jadad score for trials ranged from one to five. Four trial reports described an appropriate method of randomization,[95,96,163,175] while five reported an appropriate method of double blinding.[95,96,133,162,175] Allocation concealment was reported to be adequate in three trials.[95,96,175]

All trials where conducted in North America.

DRAFT

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 co-administration of different lipid-modifying agents (i.e. a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

A total of six trials, one of crossover design, randomizing 770 participants compared statin plus niacin combination therapy with statin monotherapy and reported one or more of clinical outcomes, serious adverse events and cancer (Table 22).[95,96,133,151,175,176] There were no trials exclusively in females, or participants of Asian, Hispanic, and/or African descent.

Reporting of participants' ethnic background was as follows:

- European descent: 4 trials, Mean = 87% (range, 82%-90%)
- Asian descent: 3 trials, Mean = 3% (range, 2%-4%)
- Hispanic descent: 3 trial, Mean = 4% (range, 1%-6%)
- African descent: 3 trial, Mean = 8% (range, 5%-13%)

Trial duration ranged from 12-52 weeks with an average of 26 weeks. Although no trial totally excluded females, on average 34% of participants were women (range, 9-48%). The average of mean ages of participants was 59 years (range of mean age, 53 to 67 years). Five trials recruited outpatients,[95,96,133,175,176] while one trial did not report recruitment setting. The mean Jadad score was 3.5 (range, 1-5) and three trials had adequate allocation concealment.[95,96,175]

Of these five trials, none were exclusively in participants requiring intensive lipid lowering treatment (i.e. participants with established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL.

Outcomes with no available evidence

No analyzable data was available regarding participants with myocardial infarction, non-fatal myocardial infarction, cerebrovascular events, hemorrhagic stroke, ischemic stroke, transient ischemic attack, carotid endarterectomy, percutaneous coronary interventions, coronary artery bypass graft and/or unspecified revascularization procedures.

Longer term outcomes

Participants with all-cause mortality: Niacin-statin combination versus statin monotherapy

All cause mortality was reported for four trials,[95,96,151,175] two of which were 24 weeks or longer in duration and which provided analyzable data (Table 22, Figure 47).[96,151] Data from the other two trials were not analyzable because there were no events.[96,175] In addition, three trials were considered to be of adequate allocation concealment,[95,96,175] two of which were 24 weeks or longer in duration and provided analyzable data.[96,175] Pooling of these two trials demonstrated no significant differences in mortality between the two groups (OR = 1.08; 95% CI = 0.17, 6.72) based on five events.

Participants with vascular death: Niacin-statin combination versus statin monotherapy

Vascular death was reported for two trials,[133,176] one of which had a followup duration of 24 weeks or more (Table 22).[133] Both had an unclear form of allocation concealment. One study had

no analyzable data,[176] while the other demonstrated no statistically significant difference in the incidence between the two groups (OR = 0.53; 95% CI = 0.03, 8.64) based on two events.[133]

Participants with fatal myocardial infarction: Niacin-statin combination versus statin monotherapy

Fatal myocardial infarction was reported for two trials, one of which reported no events so had no analyzable data (Table 22).[176] The other study, with a followup duration of 28 weeks, demonstrated no statistically significant difference in the incidence between the two groups (OR 1.63; 95% CI 0.07, 40.51), based upon one event.[96]

Participants with stroke: Niacin-statin combination versus statin monotherapy

Stroke was reported for one trial, which had a followup duration of 52 weeks (Table 22).[175]The study demonstrated no statistically significant difference in the incidence between the two groups (OR = 0.30; 95% CI = 0.01, 7.47), based upon one event.

Participants with acute coronary syndrome: Niacin-statin combination versus statin monotherapy

Acute coronary syndrome was reported for one trial, which had a followup duration of 52 weeks (Table 22).[175]The study demonstrated no statistically significant difference in the incidence between the two groups (OR 0.91; 95% CI 0.12, 6.62), based upon four events.

Participants with percutaneous coronary intervention: Niacin-statin combination versus statin monotherapy

Percutaneous coronary intervention was reported for one trial, which had a followup duration of 52 weeks (Table 22).[175] The study demonstrated no statistically significant difference in the incidence between the two groups (OR = 3.78; 95% CI = 0.41, 34.68), based upon five events.

Participants with serious adverse events: Niacin-statin combination versus statin monotherapy

Serious adverse events were reported for three trials,[95,96,151] one of which had a followup duration of 28 weeks (Table 22, Figure 48).[96] Pooling of the trial data demonstrated no statistically significant difference in the incidence between the two groups (OR 1.63; 95% CI 0.48, 5.56), based upon fourteen events. In the long-term trial,[96] there was no statistically significant difference in the incidence between the two groups (OR 1.35; 95% CI 0.25, 7.19), was based on seven events.

Participants with cancer: Niacin-statin combination versus statin monotherapy

Cancer was reported for one trial (Table 22).[96]The study followed up 175 participants for 28 weeks. The data demonstrated no statistically significant difference in the incidence between the two groups (OR = 0.10; 95% CI = 0.00, 2.20), based upon two events.

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Key Question 2: Do these regimens differ in reaching LDL-c targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

A total of twelve trials, none of crossover design, randomizing 1937 participants compared statin plus niacin combination therapy with statin monotherapy and reported one or more of the following outcomes: participants reaching LDL-targets and/or other surrogate markers, short-term side effects, tolerability, and/or adherence to treatment (Table 23-28).[40,95,96,122,133,138,151,162-164,168,175] There were no trials exclusively in females, or participants of Asian, Hispanic, and/or African descent.

Reporting of participants' ethnic background was as follows:

- European descent: 8 trials, Mean = 87% (range, 82%-94%)
- Asian descent: 3 trials, Mean = 3% (range, 2%-4%)
- Hispanic descent: 3 trial, Mean = 4% (range, 1%-6%)
- African descent: 4 trial, Mean = 4% (range, 0%-6%)

Trial duration ranged from 6 to 52 weeks, with an average of 21 weeks. Although no trial totally excluded the female gender, on average 37% of participants were women (range, 9%-50%). The average of mean ages of participants was 58 years (range of mean age, 51-67 years). Eight trials recruited outpatients,[40,95,96,122,133,138,163,175] while four trials did not report recruitment setting. The mean Jadad score was 2.7 (range, 1-5) and three trials had adequate allocation concealment.[95,96,175]

Of these twelve trials, only one was exclusively in participants requiring intensive lipid lowering treatment (i.e. participants with established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL),[175]

Outcomes with no available evidence

No data from the trials was available regarding carotid plaque area, plaque volume and/or calcification, or coronary plaque area, plaque volume, measure of stenois or calcification.

Surrogate outcomes

Niacin/ lower-dose statin combination therapy compared with higher dose statin monotherapy

One study presented data for the lower dose statin plus niacin combination therapy compared with higher dose statin monotherapy (Table 24, 25).[138] This trial compared rosuvastatin 40 mg montherapy with rosuvaststin 10 mg + extended release niacin 2g. For the surrogate outcomes, data was available for the analyses of percentage change from baseline, for LDL-c and HDL-c. Combination therapy increased the percentage changes significantly for LDL-c (MD 12.00; 95% CI 2.36, 21.74) and HDL-c (MD 12.00; 95% CI 2.26, 21.74).

In this study, there were no instances of elevated serum AST and/or ALT greater than 3 times the upper limit of normal and/or hepatitis, or CPK greater than 10 times the upper limit of normal (Table 29). However, treatment adherence was significantly lower with statin plus niacin combination therapy than with statin monotherapy (OR 0.40, 95% CI 0.19, 0.84).

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Participants reaching the ATP-III targets: Niacin-statin combination versus statin monotherapy

The incidence of participants reaching their ATP-III targets was reported for one trial (Table 23).[40] This trial compared a fixed dose combination of lovastatin and extended release niacin with atorvastatin and also with simvastatin. Two balanced pairs of treatment groups were analysed (e.g. Bays (2003_1) and Bays (2003_2)). The results for each of the two comparisons did not show any statistically significance between the two groups but the two comparisons were not pooled because of marked heterogeneity ($I^2 = 63$).

LDL-c: Niacin-statin combination versus statin monotherapy

The surrogate outcome LDL-c was reported for nine trials randomizing 1327 participants. Four presented post-treatment means/ change scores,[122,163,168,175] while six presented percentage changes from baseline (Table 24, Figure 49).[95,96,122,138,162,164] Pooling of the studies was not possible for LDL-c post-treatment means/ change scores due to marked heterogeneity ($I^2 = 52\%$) but the differences in decrease in LDL-c ranged from -1 mg/dL to -11 mg/dL, favoring the niacin plus statin combination. All studies were in a mixed population of participants, and followup duration ranged from 6 to 52 weeks.

Pooling of studies was also not possible for LDL-c percentage change from baseline due to marked heterogeneity ($I^2 = 85\%$), but differences in LDL-c percentage changes ranged from -25% to 9% with a trend in favor of statin plus niacin combination therapy (Figure 50). All studies were in a mixed population of participants, and followup duration ranged from 12 to 28. No asymmetry was evident on the funnel plot (Figure 50).

HDL-c: Niacin-statin combination versus statin monotherapy

HDL-c was reported for eight trials, three of which presented data for post-treatment means/ change score,[163,168,175] five of which presented data for the percentage change from baseline (Table 25).[95,96,122,138,162]

Pooling of the studies reporting HDL-c post-treatment means/ change score yielded a significantly greater increase in HDL-c post-treatment with statin plus niacin combination therapy than with statin monotherapy among 216 participants (MD = 7.13 mg/dL; 95% CI = 3.84 mg/dL, 10.42 mg/dL). Pooling of the studies reporting HDL-c percentage change from baseline was not possible due to marked heterogeneity ($I^2 = 79\%$) but differences in HDL-c percentage changes ranged from 6% to 24% in favor of statin plus niacin combination therapy. All studies were in a mixed population of participants, and followup duration ranged from 12 to 28 weeks.

TC:HDL-c ratio: Niacin-statin combination versus statin monotherapy

The surrogate outcome, TC:HDL-c ratio was reported for two trials (Table 26).[122,168] The TC:HDL-c ratio was significantly lower following statin plus niacin combination therapy than with statin monotherapy, when measured both as post-treatment means/ change score (MD = -1.58; 95%CI = -2.18, -0.98),[168] and as percentage change from baseline (MD = -6.00%; 95%CI = -9.60%, -2.40%).[122]

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CIMT: Niacin-statin combination versus statin monotherapy

The surrogate outcome, carotid intima-media thickness (CIMT), was reported for one trial, as post-treatment means/ change score (Table 27).[175] Statin plus niacin combination therapy was marginally more effective than statin monotherapy in reducing the rate of increase in CIMT (MD = -0.03 mm; 95% CI = -0.06 mm, 0.00 mm).

Participants' adherence to treatment: Niacin-statin combination versus statin monotherapy

Treatment adherence was reported for five trials (Table 28).[40,122,138,162,175] Pooling of the studies demonstrated no significant difference in the incidence between the groups treated with combination therapy or monotherapy (OR = 0.79, 95% CI = 0.50, 1.27). Two of the trials has follow-up 24 weeks or longer.[138,175] Pooling of the studies demonstrated no significant difference in the incidence between the groups treated with combination therapy or monotherapy (OR = 0.64, 95% CI = 0.25, 1.61).

Participants with an adverse event: Niacin-statin combination versus statin monotherapy

Total adverse events were reported for four trials (Table 28),[95,96,138,162] which were not pooled due to marked heterogeneity (I^2 = 57%). The trials had similar followup periods (20 to 28 weeks) and all were in a mixed population. Two of the trials has follow-up 24 weeks or longer, but were not pooled due to marked heterogeneity (I^2 = 63%).[96,138]

Participants withdrawing due to adverse events: Niacin-statin combination versus statin monotherapy

Withdrawals due to adverse events was reported for eight trials (Table 28, Figure 51).[40,95,96,133,151,162,168,175] Pooling of the studies demonstrated a significantly higher incidence of withdrawals in the combination group (OR = 2.24, 95% CI = 1.37, 3.68).

Participants with AST and/or ALT above 3 times the upper limit of normal and/or hepatitis: Niacin-statin combination versus statin monotherapy

Elevated serum AST and/or ALT above 3 times the upper limit of normal and/or hepatitis was reported for seven trials,[40,95,133,138,151,162,175] four of which reported events and therefore provided analyzable data (Table 28).[95,133,151,162] Pooling of the studies demonstrated no significant difference in the incidences between the two groups (OR = 1.17, 95% CI = 0.27, 5.17) based upon 11 events in 1223 participants.

Participants with myalgia: Niacin-statin combination versus statin monotherapy

Incidence of myalgia was reported for three trials.[40,96,133] Pooling of the studies demonstrated a non-significant difference in the incidence of myalgia in both groups (OR = 0.45, 95% CI = 0.19, 1.07), based upon 22 events in 665 participants.

Participants with CPK above 10 times the upper limit of normal: Niacin-statin combination versus statin monotherapy

The incidence of CPK greater than 10 times the upper limit of normal was reported in seven trials with no events identified for 1272 participants for the trials' respective follow-up durations (Table 28). [40,95,96,122,138,151,162]

Participants with rhabdomyolysis: Niacin-statin combination versus statin monotherapy

Rhabdomyolysis was reported not to have occurred in two trials (Table 28).[95,96]

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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: Niacin-statin combination versus statin monotherapy

Incidence of all cause mortality was reported for one trial, for the subgroup populations all participants with vascular disease, and participants requiring intensive lipid lowering therapy (Table 22).[175] There was no statistically significant difference between the two groups (OR 0.53; 95% CI 0.03, 8.64) for both subgroups.

Vascular death: Niacin-statin combination versus statin monotherapy

The incidence of vascular death was reported for one trial, for participants requiring intensive lipid lowering therapy, and specifically for those with established vascular disease (Table 22).[176] No events were recorded, so the outcomes were not analyzable.

ATP-III: Niacin-statin combination versus statin monotherapy

The surrogate outcome, participants reaching their ATP-III target, was reported for one trial, for participants requiring intensive lipid lowering therapy, and specifically for those with established vascular disease (Table 23).[40] There was no statistically significant difference between the two groups (OR 1.51; 95% CI 0.56, 4.08) for both subgroups.

LDL-c: Niacin - statin combination versus statin monotherapy

The surrogate outcome LDL-c measured as post-treatment means/ change score was reported for one trial, for participants requiring intensive lipid lowering therapy, and specifically for those with established vascular disease (Table 24).[175] Statistically significantly higher LDL-c was seen in the combination therapy group (MD = -1.00; 95% CI = -8.32, 6.32) for both subgroups.

HDL-c: Niacin - statin combination versus statin monotherapy

The surrogate outcome HDL-c measured as post-treatment means/ change score was reported for one trial, for participants requiring intensive lipid lowering therapy, and specifically for those with established vascular disease and a subgroup also who were diabetics (Table 25).[175] In participants with established vascular disease, there was a statistically significant increase in HDL-c in the statin-niacin combination as compared with statin monotherapy (MD = 7.00; 95% CI = 2.78, 11.22). In a subgroup of participants with diabetes mellitus[175], there was a statistically significant increase in HDL-c in the statin-niacin combination as compared with statin monotherapy (MD = 7.00; 95% CI = 4.02, 9.98).

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Tables and Figures: Niacin-statin Combination Therapy versus Statin Monotherapy

Table 22. Quantitative syntheses of longer term outcomes (clinical, serious adverse events and cancer) for niacin plus statin therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant treatment groups	Number of Events	Odds ratio	Lower CI	Upper CI
All-cause mortality						
All trials[95,96,151,175]	4	577	5	1.08	0.17	6.72
Trials with adequate allocation concealment[95,96,175]	3	457	5	1.08	0.17	6.72
Participants with vascular disease [175]	1	149	3	1.84	0.16	20.76
Vascular death						
All trials[133,176]	2	229	2	0.53	0.03	8.64
Participants with vascular disease [176]	1	58	0			
Fatal myocardial infarction						
All trials[96,176]	2	229	1	1.63	0.07	40.51
Any stroke						
All trials[175]	1	149	1	0.30	0.01	7.47
Acute coronary syndrome						
All trials[175]	1	149	4	0.91	0.12	6.62
Percutaneous coronary intervention						
All trials[175]	1	149	5	3.78	0.41	34.68
Serious adverse events						
All trials[95,96,151]	3	428	14	1.63	0.48	5.56
Cancer						
All trials[96]	1	175	2	0.10	0.00	2.20

Abbreviations: CI = 95% confidence interval

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Table 23. Quantitative syntheses of the incidence of participants achieving ATP-III LDL-c targets, for niacin plus statin therapy compared with statin monotherapy

	Number of trials	Dose Niacin (mg/day)	Number of participants in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Relative probability of attaining ATPIII target							
All trials[40]	1	2000	222	166			
Participants with vascular disease - Participants requiring intensive lipid lowering therapy[40]	1	2000	66	40	1.51	0.56	4.08

Abbreviations: ATP III = the third Adult Treatment Panel III Adult Treatment Panel of the National Cholesterol Education Program, CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

Table 24. Quantitative syntheses of LDL-c data, for niacin plus statin combination therapy compared with statin monotherapy

	Number of trials	Number of participants in relevant treatment groups	Point Estimate	Lower CI	Upper CI
Difference in mean LDL-c - change from baseline (mg/dL)					
All trials[122,163,168,175]	4	349	-	-	-
Participants in need of intensive lipid lowering therapy – all with established vascular disease[175]	1	149	-1.00	-8.32	6.32
Difference in mean percentage change from baseline (%)					
All trials[95,96,122,138,162,164]	6	590	-	-	-
Rosuvastatin - Lower dose statin in combination versus higher dose monotherapy[138]	1	124	12.00	2.26	21.74

AbbreviationsCI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

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Table 25. Quantitative syntheses of HDL-c data, for niacin plus statin combination therapy compared with statin monotherapy

Population	Number of trials	Number of participants in relevant treatment groups	Point Estimate	Lower CI	Upper CI
Difference in mean HDL-c - change from baseline (mg/dL)					
All trials[163,168,175]	3	216	7.13	3.84	10.42
Participants requiring intensive lipid lowering therapy Participants with vascular disease[175]	1	149	7.00	2.78	11.22
Participants requiring intensive lipid lowering therapy Participants diabetes mellitus[175]	1	41	7.00	4.02	9.98
Difference in mean percentage change from baseline					
All trials[95,96,122,138,162]	5	649	-	-	-
Rosuvastatin Lower dose statin in combination compared with higher dose monotherapy [138]	1	117	12.00	2.26	21.74

Abbreviations: CI = 95% confidence interval, HDL-c = high density lipoprotein cholesterol

Table 26. Quantitative syntheses of total cholesterol:HDL-c ratios, for niacin plus statin combination therapy compared with statin monotherapy

Population	Number of trials	Number of participants in relevant treatment groups	Max dose niacin (mg/d)	Point estimate	Lower CI	Upper CI
Difference in changes in mean TC: HDL-c ratio (mg/dL)						
All trials[168]	1	39	3000	-1.58	-2.18	-0.98
Difference in mean percentage change in TC: HDL-c ratio (%)						
All trials[122]	1	198	2000	-6.00	-9.60	-2.40

Abbreviations: CI = 95% confidence interval, HDL-c = high density lipoprotein cholesterol, TC = total cholesterol

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Table 27. Quantitative synthesis of CIMT data, for niacin plus statin combination therapy compared with statin monotherapy

	Number of trials	Number of participants in relevant treatment groups	Max dose niacin (mg/d)	Point estimate	Lower CI	Upper CI
Difference in mean CIMT						
All trials[175]	1	198	2000	-0.03	-0.06	0.003

Abbreviations: CI = 95% confidence interval, CIMT = carotid intima-medial thickness

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Table 28. Quantitative syntheses of short term harms and adherence to treatment, for niacin plus statin combination therapy compared with statin monotherapy

Population	Number of trials	Niacin Dose (mg/d)	Number of participants in relevant treatment groups	Number of events	Odds ratio	Lower CI	Upper CI
Relative probability of participants adhering to treatment							
All trials[40,122,138,162,175]	5	1000 - 2500	1011	851	0.79	0.50	1.27
Rosuvastatin Lower dose statin in combination versus higher dose monotherapy[138]	1	2000	126	67	0.40	0.19	0.84
Relative probability of participants experiencing an adverse event							
All trials[95,96,138,162]	4	2000 - 2500	636	502	-	-	-
Relative probability of participants withdrawing from treatment due to an adverse event							
All trials[40,95,96,133,151,162,168,175]	8	1000 - 3000	1264	162	2.24	1.37	3.68
Relative probability of participants experiencing rhabdomyolysis							
All trials[95,96]	2	2000-2500	308	0	-	-	-
Relative probability of participants experiencing elevated serum AST and/or ALT greater than 3 times the upper limit of normal, and/or hepatitis							
All trials[40,95,133,138,151,162,175]	7	1000 - 2500	1223	11	1.17	0.27	5.17
Relative probability of participants experiencing myalgia							
All trials[40,96,133]	3	2000	665	22	0.45	0.19	1.07
Relative probability of participants experiencing CPK greater than 10 times the upper limit of normal							
All trials[40,40,95,96,122,138,151,162]	7	2000 - 2500	1272	0	-	-	-
Rosuvastatin Lower dose statin in combination versus higher dose monotherapy[138]	1	2000	126	0	-	-	-

Abbreviations: ALT = alanine transaminase, AST = aspartate transaminase, CI = 95% confidence interval, CPK = creatine phosphokinase

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Figure 47. Forest plot of all-cause mortality for niacin plus statin therapy compared with statin monotherapy, in all participants, all trials with adequate allocation concealment

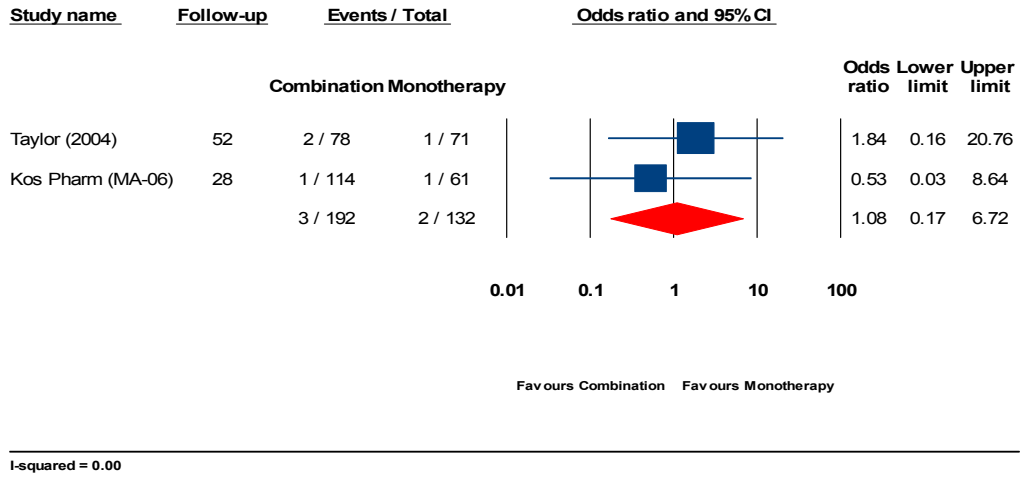

Figure 48. Forest plot of serious adverse events for niacin plus statin therapy compared with statin monotherapy, in all participants

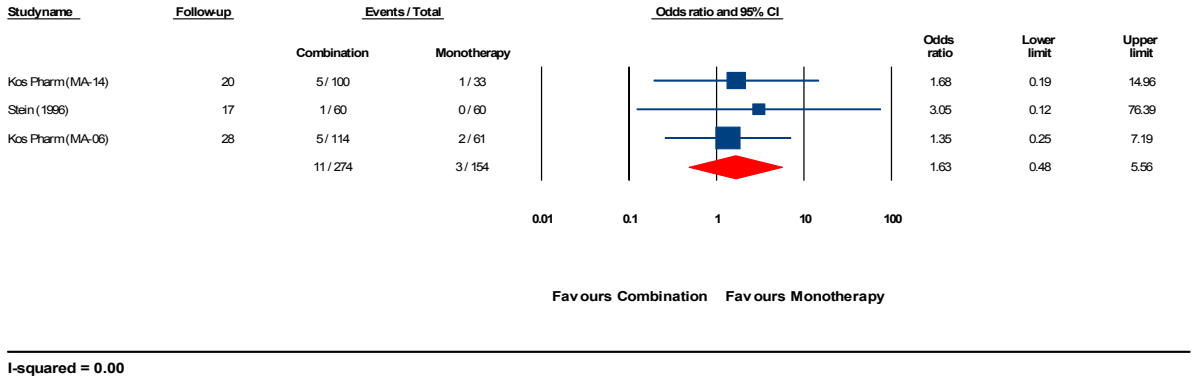

Figure 49. Forest plot of difference in LDL-c post-treatment means/mean changes scores for niacin plus statin therapy compared with statin monotherapy, in all participants

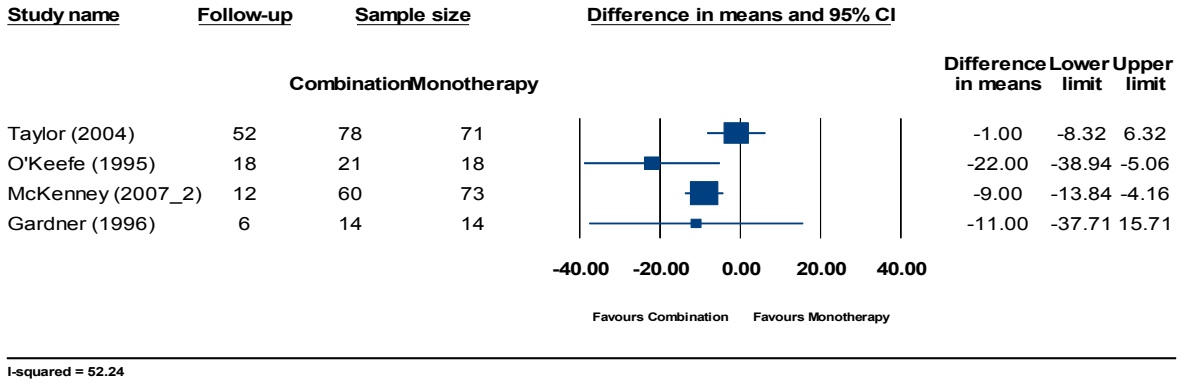

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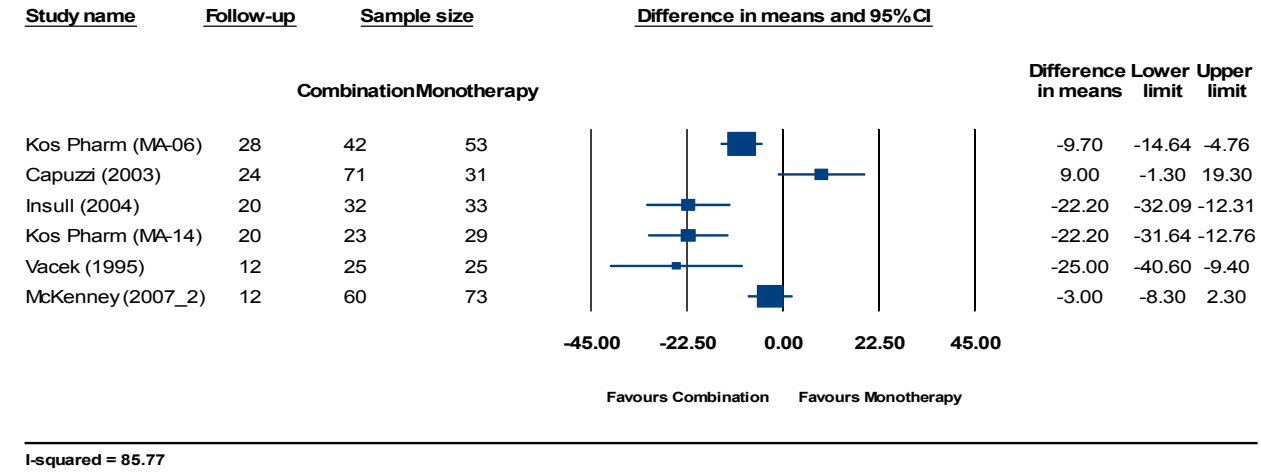
Figure 50. Forest and funnel plots of difference in LDL-c mean percentage change from baseline for niacin plus statin therapy compared with statin monotherapy, in participants requiring intensive lipid lowering therapy



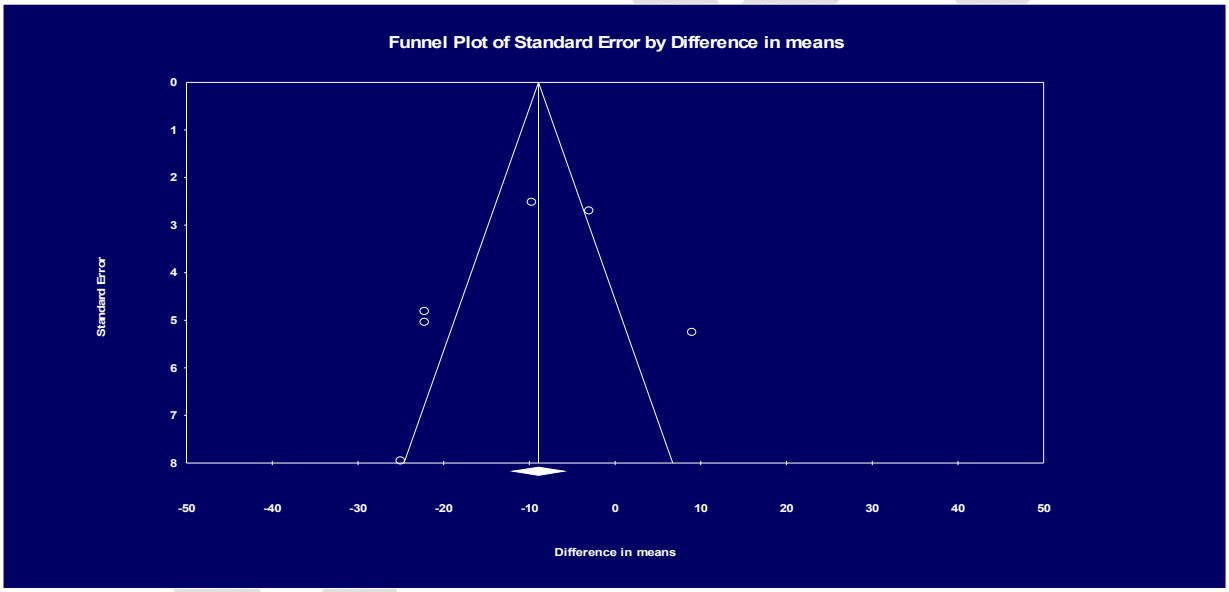
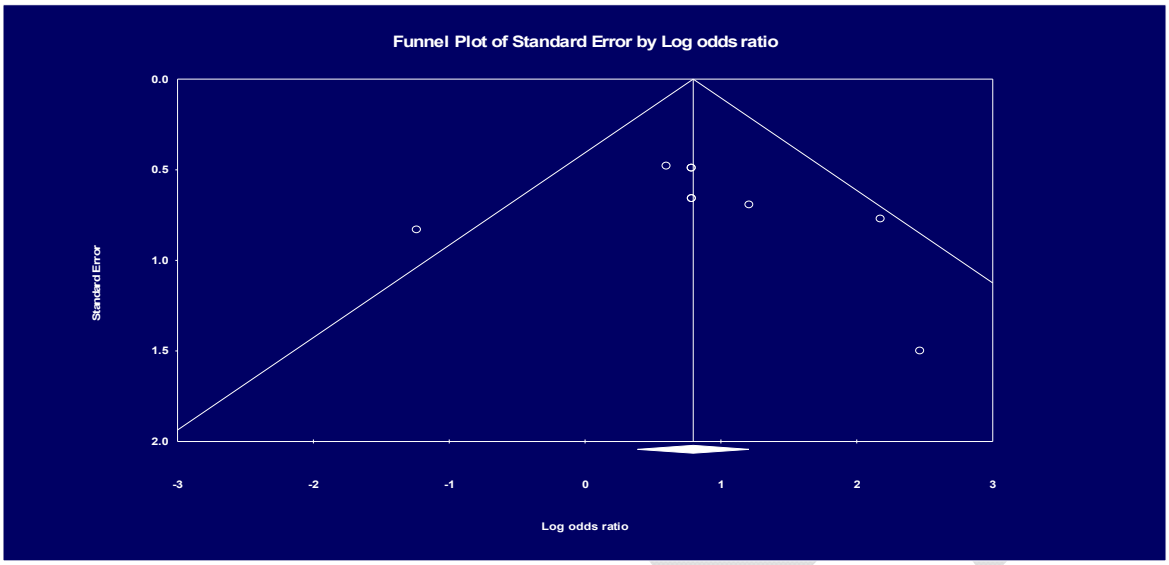


Figure 51. Funnel plot of incidence of withdrawal from treatment due to an adverse event, for niacin plus statin therapy compared with statin monotherapy, in all participants



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Bile Acid Sequestrant Combination Therapy versus Statin Monotherapy

Overview of included studies

A total of 17 RCTs evaluated the relative efficacy and/or harm of the combination of statin plus bile acid sequestrant (BAS) (cholestyramine 1.6-24 g/day, colesevelam 2.3-3.8 g/day, colestipol 1.65-20 g/day) therapy compared with statin monotherapy, in a total of 2930 participants (Table 4). In addition, two non-randomized studies addressed this comparison (Table 30).[79,80] Two trials included companion reports (Table of 6); one in the published literature, [177] and one a Federal Drug Agency report of an extension of treatment and followup for a longer period of time.[152] The longest available data for any given trial were analyzed. One companion report was considered for trial referencing.[191]

Twelve trials were conducted in multiple centers [43,101,117,139,145,152,154,165,166,169,170,177], and three in single centers.[108,144,153] Information regarding site was not reported for two trials.[99,106] Fifteen of the 17 trials were partially or completely sponsored by the pharmaceutical industry,[43,99,101,106,108,117,139,152,154,165,166,169,170,177] while funding was not disclosed for two trials.[144,145] Total Jadad scores ranged from one to five. An appropriate method of randomization was reported for three trials,[152,153,169] and appropriate methods of double blinding were reported for four trials.[101,152,153,165] Allocation concealment was deemed adequate for three trials [139,152,153] and the results of two trials were based on intention-to-treat analyses.[101,106]

Most trials (12) were carried out in North America,[43,99,101,106,108,139,144,152,165,166,170] with three trials in Europe,[117,153,169] and two trials in Australia.[154,177]

Reporting of participants' ethnicity was provided in five trials as follow

- European descent (89 to 96%)[43,139,152,165,170]
- Hispanic descent (1.3 to 1.5%)[152,165]
- African descent (3 to 8%)[43,139,152,165]
- Asian descent (3%)[165]

Neither power analyses regarding the primary outcome measures nor adjudication of outcomes were reported. Also, except for two trials,[43,170] active clinical adverse event data collection was either not reported or unclear.

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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 co-administration of different lipid-modifying agents (i.e. a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

A total of four parallel group RCTs including 511 participants compared statin plus BAS combinations and statin monotherapy, and reported one or more clinical outcomes or serious adverse events.[43,152,165,177] Three trials provided information on participants' ethnic descent.[43,152,165] In included arms of those trials, 89-95% of participants were of European descent, 3-7% of African descent, 1.5% of Hispanic descent and 2.6% of Asian descent. No trial was conducted exclusively in one gender. On average, 51% of participants were female (range 43 to 60%). The average of mean ages of participants was 54 years (range 49 to 59 years). Two trials recruited outpatients,[152,177] while two trials did not report recruitment setting.[43,165] Mean Jadad score was 3 (range, 1to 5) and one trial had adequate allocation concealment.[152] No trials were exclusively in participants requiring intensive lipid lowering therapy.

The participants in these four trials were relatively homogenous, as none of the trials were performed in high risk participants, and none reported prior statin exposure. Most trials excluded participants with triglycerides above 300-600 mg/dL, patients with recent or unstable vascular disease, uncontrolled diabetes mellitus and hypertension, liver and muscle disease or high ALT, AST and/or CPK, and/or impaired renal function. No trial employed a statin plus BAS combined pill.

Outcomes without Evidence

No RCT reported relevant data for the following outcomes: vascular death, non-fatal myocardial infarction, cerebrovascular events, ischemic or hemorrhagic stroke, transient ischemic attack, acute coronary syndrome, carotid endarterectomy, percutaneous coronary intervention, coronary arterial bypass graft or any revascularization procedure, or cancer.

Longer Term Outcomes

All-cause mortality: BAS-statin combination versus statin monotherapy

Three trials on 373 evaluable participants reported two deaths during a follow up of 4 to 24 weeks duration (Table 29).[43,152,165] Only one of these trials, on 150 participants, was based on treatment and follow up of 24 weeks.[43] This study compared fluvastatin (10-20 mg/day) and cholestyramine (16 g/day) with fluvastatin (10-20 mg/day), and reported one death.[43] Across these three trials of 4 to 24 weeks duration, two trials with 151 evaluable participants and a total of two deaths could be meta-analyzed without an evident indication of heterogeneity (Figure 52).[43,152] A nonsignificant odds ratio of 1.07 (95% CI 0.11, 10.51) was observed (Table 29). A report of one trial with adequate allocation concealment had an estimable odds ratio of 3.25 (95% CI 0.13, 82.24) (Appendix D).[152] No report permitted comparison of lower dose statin plus BAS with higher dose statin monotherapy, and none of the trials was performed specifically on participants requiring intensive lipid lowering therapy.

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Fatal Myocardial Infarction: BAS-statin combination versus statin monotherapy

One trial on 150 evaluable participants compared fluvastatin (10-20 mg/day) and cholestyramine (16 g/day) with fluvastatin (10-20 mg/day), and reported one fatal myocardial infarction on monotherapy. A nonsignificant odds ratio of 0.35 (95% CI 0.01, 8.91) was observed (Table 29) [43].

Serious Adverse Events: BAS-statin combination versus statin monotherapy

Seven participants experienced serious adverse events during two trials on 278 evaluable participants, during a followup of 6 to 30 weeks (Table 29).[152,177] Simons et al compared simvastatin (40 mg/day) plus cholestyramine (4 g/day) with atorvastatin (80 mg/day) monotherapy in 136 participants, with six serious adverse events during a followup of 30 weeks.[177] Knapp et al compared simvastatin (10-20 mg/day) plus colesevelam (2.3-3.8 g/day) with simvastatin (10-20 mg/day) monotherapy in 142 participants, with 1 serious adverse event during a 6 week trial (Appendix D).[152] The pooled nonsignificant odds ratio was 0.39 (95% CI 0.06, 2.36) (Figure 53).

Non-RCT evidence: BAS-statin combination versus statin monotherapy

Two non-randomized controlled trials compared statin plus BAS therapy with statin monotherapy (Table 30). Ojala et al [79] added colestipol (dose range from 5 to 20 g/day) to treatment of patients with primary hypercholesterolemia, some of whom had CHD. LDL-c was above 120 mg/dL in CHD patients or ≥ 140 mg/dL for those without CHD, despite the use of lovastatin (80 mg/day). The only reported outcome of interest was the absence of serious adverse events in either treatment group during the 3 year follow up.[79] Mol et al compared simvastatin (40mg/day) plus cholestyramine (4 g/day) or colestipol (5g/day), with simvastatin (40 mg/day) in 26 patients with severe familial hypercholesterolemia, for 2 years.[80] In the combination group, one participant experienced a myocardial infarction and one experienced unstable angina, but there were no cases of coronary arterial bypass graft [80]. No other outcome of interest was reported (Table 30).

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Key Question 2: Do these regimens differ in reaching LDL-targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

Records of seventeen trials comparing a statin plus BAS combination with statin monotherapy reported one or more surrogate efficacy or harm outcomes, other than serious adverse events and cancer (Table 4).[43,99,101,106,108,117,139,144,145,152-154,165,166,169,170,177] These trials included 2930 randomized participants. No trials were of crossover design. Six records provided information on participants' descent,[43,139,145,152,165,170] with reports of 87 to 96% of participants of European descent, 3 to 8% of African descent, 1.5% of Hispanic descent and 2.6% of Asian descent. Trial duration ranged from 4 to 192 weeks with an average of 32 weeks. One trial was conducted exclusively in males.[99] In the remaining 16 trials, on average 38% of participants were females (range, 5-60%). The average of mean ages of participants was 54 years (range of mean age, 45 to 62 years). Five trials recruited outpatients [101,152,169,170,177], while 12 trials did not report recruitment setting. Mean Jadad score was 2 (range, 1 to 5) and four trials had adequate allocation concealment [139,152,153,169]. Five of these trials included 426 participants requiring intensive lipid lowering treatment and/or participants with baseline LDL-c above 190 mg/dL.[99,139,144,154,177]

Three trials included only participants with familial combined hypercholesterolemia,[108,144,145] three included participants all with LDL-c above 190mg/dL,[139,144,177], two reported past history of coronary artery diseases in most or all participants,[99,154] and one reported that all participants had prior statin exposure.[139] The other seven trials were relatively homogenous regarding participants' characteristics; most trials excluded participants with TG above 300-600 mg/dL, recent or unstable vascular disease, uncontrolled diabetes mellitus or hypertension, liver and muscle disease, high ALT, AST and CPK, or impaired renal function. No trial employed a BAS plus statin combined pill.

Three trials included only participants with familial combined hypercholesterolemia,[108,144,145] three included participants all with LDL-c above 190mg/dL,[139,144,177], two reported past history of coronary artery diseases in most or all participants,[99,154] and one reported that all participants had prior statin exposure.[139] The other seven trials were relatively homogenous regarding participants' characteristics; most trials excluded participants with TG above 300-600 mg/dL, recent or unstable vascular disease, uncontrolled diabetes mellitus or hypertension, liver and muscle disease, high ALT, AST and CPK, or impaired renal function. No trial employed a BAS plus statin combined pill.

Outcomes without Evidence

No RCT reported relevant data for the following surrogate markers: TC:HDL-c ratio, carotid or coronary plaque area/volume, measure of stenosis nor calcification. In addition, no RCT reported data on the proportion of participants who developed rhabdomyolysis. Data were synthesized for all remaining outcomes.

Participants reaching LDL-c ATPIII targets: BAS-statin combination versus statin monotherapy

One record of a 12 week trial on 59 evaluable participants reported attainment of ATP III LDL-c targets (Table 31).[99] This trial compared pravastatin (20 mg/day) and cholestyramine (10 g/day) with pravastatin (40 mg/day) in 59 male North American participants all with moderate hypercholesterolemia, history of coronary artery diseases and prior use of statins. Eighteen participants reached ATP III LDL-c target levels, yielding an estimable odds ratio of 4.51 (1.34, 15.14) favoring combination therapy (Table 31, Appendix D).[99]

LDL-c post-treatment means or mean change scores: BAS-statin combination versus statin monotherapy

Nine trials yielded 10 pairs of analyzable trial arms, for 1222 evaluable participants.[101,106,144,145,152,165,166,169,170] Duration of followup ranged from 4 to 96 weeks, but the majority of trials were less than 24 weeks in length. A significant pooled mean difference of -20.78 mg/dL (95% CI -26.02 mg/dL, -15.54 mg/dL) in favor of combination therapy was observed, and the results were not significantly heterogeneous (I^2 = 39%) (Figure 54). Across trials, participants were diverse, including those who did not report previous use of statin,[106,152,169] those with familial hypercholesterolemia,[144] and those with LDL-c above190 mg/dL at baseline.[144] All but one trial [144] compared identical statins. Asymmetry was not evident on the funnel plot (Figure 54).

One trial compared atorvastatin or simvastatin (40 mg/day) plus colestipol (20 g/day) with a higher dose of atorvastatin (80 mg/day) monotherapy for 48 weeks in 47 evaluable participants with heterogeneous familial and polygenic hypercholesterolemia, who required intensive lipid lowering because LDL-c was above 190 mg/dL at baseline [144]. A nonsignificant pooled mean difference of 15.48 mg/dL (95% CI -11.14 mg/dL, 42.1 mg/dL) was observed (Table 32, Appendix D).[144]

One trial compared lower dose atorvastatin (10 mg/day) plus colesevalam (3.8 g/day) with higher dose atorvastatin (80 mg/day) monotherapy for 6 weeks in 38 evaluable participants, and yielded a nonsignificant mean difference of 7 mg/dL (95% CI -8.2 mg/dL, 22.2 mg/dL) [101] (Table 32).

LDL-c, percentage mean change from baseline: BAS-statin combination versus statin monotherapy

A total of 11 trials provided data on 15 pairs of meta-analyzable arms on 1010 evaluable participants [43,101,139,144,145,152-154,165,170,177]. Followup duration ranged from 4 to 40 weeks, with the majority of trials less than 24 weeks in duration. Across trials, participant characteristics were relatively heterogeneous, with four trials including participants with moderate to severe familial hypercholesterolemia and requiring intensive lipid lowering therapy [139,144,154,177] and/or LDL-c above190 mg/dL at baseline.[139,144,177]

Meta-analysis was not possible due to high statistical heterogeneity (I^2 = 88%). However, most trials demonstrated significant percentage reductions from baseline in favor of statin-BAS combination compared to statin monotherapy, ranging from -4% to -16% (Figure 55). In contrast, one 30 week trial in 136 participants, comparing simvastatin (40 mg/day) plus cholestyramine (4 g/day), with atorvastatin (80 mg/day) monotherapy in participants without prior exposure to statins, showed a significant difference in means of 11% (95% CI 6.45%,

15.55%) in favor of monotherapy.[177] Asymmetry was not evident on the funnel plot, and Egger's regression test was not significant (Figure 55).

Four trials contributed efficacy data to compare statin plus BAS therapy with statin monotherapy, regardless of statin dose, in those who require intensive lipid lowering (i.e. participants with baseline LDL-c above 190 mg/dL, or history of coronary artery disease).[139,144]. Persistent statistical heterogeneity prevented meta-analysis (I^2 = 89%). All trials yielded nonsignificant mean differences in percentage change from baseline LDL-c ranging from -4.1 to 11% (Figure 56, Appendix D).[139,144,154,177]

Hunninghake et al provided data comparing lower dose atorvastatin (10 mg/day) plus colesevalam (3.8 g/day) with higher dose atorvastatin (80 mg/day) monotherapy.[101] This study investigated 38 participants without any particular risk factor and reported a percentage mean difference of 0.28% (95% CI -9.02%, 9.59).

HDL-c post-treatment means or mean change scores: BAS-statin combination versus statin monotherapy

Six trials yielded analyzable data in 1481 evaluable participants.[144,145,165,166,169,170] Follow up duration ranged from 4 to 96 weeks, and three trials were more than 24 weeks in length. Pooled results showed an estimable mean difference of -0.05 mg/dL (95% CI -1.91 mg/dL, 1.80 mg/dL) and no significant heterogeneity (I^2 = 27.9%) (Table 33, Figure 58). Across trials, participant characteristics were not very diverse, including those who were statin naïve,[106,169] and those with familial hypercholesterolemia and LDL above 190 mg/dL at baseline [144]. All but one trial [144] compared identical statins, and only one trial did not use the same dose of statin in combination and monotherapy [166]. Examination of the funnel plot showed a left side asymmetry (Figure 58).

None of the trials compared lower dose statin plus BAS with higher dose statin monotherapy. In addition, only one trial yielded analyzable data for those requiring intensive lipid lowering because of baseline LDL above 190 mg/dL.[144] This 32 to 48 week trial compared atorvastatin or simvastatin (40 mg/day) plus colestipol (20 g/day) with higher dose of atorvastatin (80 mg/day) monotherapy in 47 evaluable participants with heterogeneous familial and polygenic hypercholesterolemia, and yielded a nonsignificant mean difference of 6.9 mg/dL (95% CI -0.37 mg/dL, 14.17 mg/dL) [144] (Table 33).

HDL-c, percentage mean change from baseline: BAS-statin combination versus statin monotherapy

A total of nine trials provided 10 pairs of meta-analyzable data on 911 evaluable participants [43,139,144,145,153,154,165,170,177]. Followup duration ranged from 4 to 40 weeks, and five trials were more than 24 weeks in length. Across trials, participants presented with moderate to severe familial hypercholesterolemia and/or LDL-c above190 mg/dL at baseline.[139,144,154,177] Pooled results yielded an estimable mean percentage difference of 0.33% (95% CI -1.86%, 2.52%) and no significant heterogeneity (I^2 = 29%) (Table 33, Figure 59). Asymmetry was not evident on the funnel plot (Figure 59).

Four trials contributed efficacy data comparing statin plus BAS with statin monotherapy, regardless of statin dose, in those requiring intensive lipid lowering therapy.[139,144,154,177] Pooled results showed an estimable mean percentage difference of 2.25% (95% CI -0.56 mg/dL, 5.06 mg/dL) and no significant heterogeneity (I^2 = 3%) (Table 33, Appendix D). None of the trials

provided evaluable data comparing lower dose combination statins with higher dose monotherapy.

Measures of Adherence and Harm

Participants adherence to treatment: BAS-statin combination versus statin monotherapy

Five trials of 4 to 96 weeks duration provided analyzable data in 1420 evaluable participants.[101,117,139,145,169] Data could not be pooled because of significant heterogeneity (I^2 = 53%) (Table 34, Appendix D). One long term trial (96 weeks) compared pravastatin (20 mg/day) plus cholestyramine (8 g/day) with pravastatin (20-40 mg/day) monotherapy, in 1073 evaluable participants, and showed a significant odds ratio of 0.41 (95% CI 0.26, 0.7) in favor of monotherapy.[169] Four trials with less than 24 months followup yielded odds ratios ranging from 0.1 to 0.97.[101,117,139,145]. Two trials compared lower dose statin plus BAS with higher dose statin monotherapy:[101,117]: one 4 to 12 week trial compared simvastatin (20 mg/day) plus colestipol (5-10 g/day) with higher dose simvastatin (40 mg/day) monotherapy in 81 evaluable healthy participants, and yielded a nonsignificant odds ratio of 0.33 (95% CI 0.09, 1.27);[117] a second trial compared atorvastatin (10 mg/day) and colesevelam (3.8 g/day) with higher dose of atorvastatin (80 mg/day) as monotherapy in 39 evaluable participants, and showed a nonsignificant odds ratio of 0.94 (95% CI 0.12, 7.48) (Table 34).[101]

Participants with at least one adverse event: BAS-statin combination versus statin monotherapy

Four 4 to 24 week trials provided 6 pairs of analyzable arms including 522 evaluable participants, reporting 301 adverse events.[43,117,139,152] One long term trial (24 weeks) compared in its four arms fluvastatin (10 and 20 mg/day) plus cholestyramine (8 to 16 g/day) with fluvastatin (10 and 20 mg/day) monotherapy in 150 evaluable participants, and showed a pooled significant odds ratio of 5.14 (2.39, 11.07) in favor of monotherapy.[43] (Table 34). It is worth noting that doses of BAS varied among trials. In particular, cholestyramine was employed in combination with statins in doses varying from 1.6 g/day [139] to 16 g/day.[43] Only one 4 to12 week trial compared simvastatin (20 mg/day) and colestipol (5-10 g/day) with higher dose simvastatin (40 mg/day) as monotherapy, in 83 evaluable healthy participants, and showed a nonsignificant odds ratio of 1.19 (95% CI 0.47, 3.02) (Table 34).[117]

Participants withdrawing due to adverse event: BAS-statin combination versus statin monotherapy

Eight 4 to 24 week trials provided 9 pairs of analyzable arms in 966 evaluable participants, with 31 withdrawals due to adverse events [43,101,139,145,152,165,170,177]. Pooled results showed an estimable odds ratio of 2.77 (1.16, 6.6) in favor of monotherapy and no significant heterogeneity (I^2 = 0%) (Table 34, Appendix D). Asymmetry is not evident on the funnel plot (Figure 60). Doses of BAS varied widely among trials. Cholestyramine was administered in four trials in doses varying from 1.6 to 24 g/day;[43,139,170,177] colesevalam was administered in three trials, in doses from 2.3 to 3.8 g/day;[101,152,165] and colestipol was administered in one trial at 1.65 g/day [145].

One 4 week trial compared atorvastatin (10 mg/day) plus colesevalam (3.8 g/day) with atorvastatin (80 mg/day) monotherapy in 39 evaluable participants. There were 2 withdrawals due to adverse events, with a nonsignificant odds ratio of 1.06 (95% CI 0.06, 18.17) [117] (Table 34).

Participants with AST and/or ALT above 3 times the upper limit of normal, and/or hepatitis: BAS-statin combination versus statin monotherapy

Two 4 to 30 week trials in 212 evaluable participants reported no cases of elevated AST/ALT above three times the upper limit of normal (Table 34, Appendix D).[165,177]

Participants with myalgia: BAS-statin combination versus statin monotherapy

Four 4 to 12 week trials reported 11 cases of myalgia among 343 evaluable participants (Table 34, Appendix D).[99,139,153,165] A nonsignificant odds ratio of 0.43 (95% CI 0.12, 1.54), without evidence of significant heterogenity ($I^2 = 0\%$) was observed. No trials with estimable data enabled comparison of lower dose of statin with BAS versus higher dose of the same statin monotherapy.

Participants with CPK ≥ 10 times the upper limit of normal: BAS-statin combination versus statin monotherapy

Two 6 to 30 week trials in 283 evaluable participants reported no cases of elevated CPK above 10 times the upper limit (Table 34, Appendix D).[139,177]

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Key Question 3: Compared with higher-dose statins, and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

Surrogate outcomes

The only available data for subgroups of interest were the proportion of participants reaching LDL-c ATPIII targets in those with established vascular diseases,[99] and changes in LDL-c and HDL-c for participants with baseline LDL-c above 190 mg/dL.[139,144,177]

Participants reaching LDL-c ATPIII targets: BAS-statin combination versus statin monotherapy

Participants with established vascular diseases: A single 12 week trial in 59 evaluable participants reported attainment of ATP III LDL-c targets (Table 31).[99] This trial compared pravastatin (20 mg/day) and cholestyramine (10 g/day) with pravastatin (40 mg/day) in 59 male North American participants, all with moderate hypercholesterolemia, a history of coronary artery disease and prior use of statins. Eighteen participants reached ATP III LDL-c target levels, yielding an estimable odds ratio of 4.51 (1.34, 15.14) favoring combination therapy (Table 31, Appendix D).[99]

LDL-c, post-treatment means or mean change scores in participants with baseline LDL-c above 190 mg/dL: BAS-statin combination versus statin monotherapy

One trial in 37 evaluable participants comparing 40mg/day of atorvastatin or simvastatin plus 20 g/day of colestipol with 80 mg/day of atorvastatin monotherapy was conducted in participants with baseline LDL-c above 190 mg/dL.[144] This trial was of 32 weeks duration and showed a nonsignificant mean difference of 15.48 mg/dL (95% CI -11.14 mg/dL; 42.1 mg/dL).

LDL-c, percentage mean change from baseline in participants with baseline LDL-c above 190 mg/dL: BAS-statin combination versus statin monotherapy

Three trials contributed efficacy data for statin plus BAS combination therapy in comparison with statin monotherapy, regardless of statin dose, in participants with baseline LDL-c above 190 mg/dL [139,144,177]. Statistical heterogeneity prevented meta-analysis (I-squared = 78%). All trials showed nonsignificant mean differences in percentage change from baseline in LDL-c (Figure 57): one 6 week trial in 144 evaluable participants employing identical high dose of rosuvastatin in combination and as monotherapy had a mean percentage reduction of -4.1% (-9.1, 0.9) [139]; one 48 week trial on 37 evaluable participants compared 40mg/day of atorvastatin or simvastatin plus 20 g/day of colestipol with 80 mg/day of atorvastatin as monotherapy and had a mean percentage reduction of 5.4% (95% CI -1.84, 12.67%);[144]and a 30 week trial in 136 evaluable participants compared 40mg/day of simvastatin plus 4 g/day of cholestyramine with 80 mg/day of atorvastatin monotherapy, and had a mean percentage reduction of 11% favouring monotherapy (95% CI 6.45%, 15.55%).[177]

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HDL-c, post-treatment means or mean change scores in participants with baseline LDL-c above 190 mg/dL: BAS-statin combination versus statin monotherapy

A single 32 week trial provided information on 37 evaluable participants presenting with baseline LDL-c above 190 mg/dL [144]. A nonsignificant mean difference of 6.9 mg/dL (95% CI -0.37 mg/dL; 14.17 mg/dL) was observed.

HDL-c, percentage mean change from baseline in participants with baseline LDL-c above 190 mg/dL: BAS-statin combination versus statin monotherapy

The same four trials described above for percentage changes in LDL-c also provided data on mean percentage change in HDL-c.[139,144,177] Pooled results showed an estimable mean percentage difference of 2.37% (95% CI -1.18 %, 5.93%) and no significant heterogeneity (I^2 = 2%)(Table 33).

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Tables and Figures: Bile Acid Sequestrant - Statin Combination Therapy Compared With Statin Monotherapy

Table 29. Quantitative syntheses of longer term outcomes data (clinical, serious adverse events and cancer) for BAS plus statin therapy compared with statin monotherapy

Outcome	Number of trials reporting outcome	Number of participants in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
All-cause mortality						
All trials[43,152,165]	3	373	2	1.07	0.11	10.51
All trials 24 weeks or more followup[43]	1	77	1	0.35	0.01	8.9
Trials with adequate allocation concealment [152]	1	147	1	3.25	0.13	82.24
Fatal Myocardial Infarction						
All trials Trial 24 weeks[43]	1	150	1	0.35	0.01	8.91
Serious Adverse Event(s)						
All trials[152,177]	2	278	7	0.39	0.06	2.36

Abbreviations: BAS = bile acid sequestrant, CI = 95% confidence interval

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Table 30. Non-randomized controlled trial evidence regarding BAS plus statin therapy compared with statin monotherapy

Trial	Design Duration Downs and Black score	Patients (LDL-c mg/dL)	Monotherapy Dose (mg/d)	Combination Therapy Dose (mg/d)	Results	Limitations	Applicability	Conclusion
Ojala (1990) [79]	CCT 3 years 16/28	54 men and postmenopausal women less than 70 y with 1° HC, with or without CHD, and without marked hypertriglyceridemia who had previously participated in a lovastatin-probucol RCT Baseline LDL-c (SD) combination 395 (66)mg/dL mono 240 (39)mg/dL	Lovastatin (max 80mg/d) Titrated in CHD if LDL-c ≥ 120 mg/dL Titrated in others if LDL-c ≥ 140 mg/dL	In patients with LDL-c still above target, colestipol was added and titrated to maximal tolerated dose – lovastatin (80, average dose 74), colestipol (maximum dose 2000, average dose 1200)	Mortality and other clinical outcomes of interest, cancer and cognitive decline NR SAE: Zero patients with in both treatment groups	Groups were not comparable based on type of hypercholesterolemia: non-familial hypercholesterolemia mono, familial hypercholesterolemia combination	Low event rate and lack of reporting of other important long-term outcomes, unknown setting, and patient population are suggestive of low applicability	No comparative analysis can be made given different patient subtypes in the two arms

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Trial	Design Duration Downs and Black score	Patients (LDL-c mg/dL)	Monotherapy Dose (mg/d)	Combination Therapy Dose (mg/d)	Results	Limitations	Applicability	Conclusion
Mol (1990) [80] NR NR	CCT 2 years 13/28	26 patients with severe familial hypercholesterolemia Baseline LDL-c (SD) = 342 (68.5)	Simvastatin 40	S 40 plus C-amine 4000 or colestipol 5000	Mortality and other clinical outcomes of interest, SAE, cancer and cognitive decline NR Myocardial infarction: S40 = 0/12; S40+BAS =1/14 Unstable angina: MI: S40 = 0/12; S40+BAS =1/14 CABG: MI: S40 = 0/12; S40+BAS =2/14	No comparison of baseline characteristics was reported	Low event rate, lack of reporting of other important long-term outcomes, unknown setting, and absence of reporting of exclusion criteria are suggestive of low applicability	Results inconclusive given low event rate and lack of statistical significance

Abbreviations: BAS = bile acid sequestrant, CABG = coronary arterial bypass graft, C-amine = colestyramine, CCT = clinical controlled trial, CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol, N = number, S = simvastatin, SAE = serious adverse events, TG = triglycerides

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Table 31. Quantitative syntheses of participants attaining ATP III LDL-c targets, for BAS plus statin therapy compared with statin monotherapy

Outcome	Number of trials reporting outcome	Number of participants in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Relative probability of attaining ATPIII LDL-c goal						
All trials						
Participants requiring intensive lipid lowering therapy	1	59	18	4.51	1.34	15.14
All participants with established vascular diseases [99]						

Abbreviations: ATP III = Third Adult Treatment Panel of the National Cholesterol Education Program, BAS = bile acid sequestrant, CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

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Table 32. Quantitative syntheses of LDL-c data, for BAS plus statin therapy compared with statin monotherapy

Quantitative syntheses	Number of trials reporting outcome	Number in relevant treatment groups	Point Estimate	Lower CI	Upper CI
Difference in mean LDL-c post-treatment / change score from baseline (mg/dL)					
All trials [101,106,144,145,152,165,166,169,170]	9	1222	-20.78	-26.02	-15.54
Lower dose statin in combination versus higher dose monotherapy [101]	1	38	7.00	-8.20	22.20
Participants in need of intensive lipid lowering therapy Participants with LDL-c>190 mg/dL [144]	1	47	15.48	-11.14	42.10
Difference in mean LDL-c percentage change from baseline					
All trials [43,43,101,139,144,145,152,152-154,165,170,177]	11	1010			
Atorvastatin Lower dose statin in combination versus higher dose monotherapy [101]	1	38	5	-3.34	13.34
Participants in need of intensive lipid lowering therapy [139,144,154,177]	4	367			
Participants with LDL-c>190 [139,144,177]	3	317			

Abbreviations: BAS = bile acid sequestrant, CI = 95% confidence interval, LDL-c = low density lipoprotein cholesterol

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Table 33. Quantitative syntheses of HDL-c data, for BAS plus statin therapy compared with statin monotherapy

Quantitative syntheses	Number of trials reporting outcome	Number in relevant treatment groups	Point Estimate	Lower CI	Upper CI
Difference in mean HDL-c post-treatment / change score from baseline (mg/dl)					
All trials [144,145,165,166,169,170]	6	1481	-0.05	-1.91	1.80
Participants requiring intensive lipid lowering therapy Participants with LDL-c>190 mg/dL [144]	1	37.00	6.90	-0.37	14.17
Difference in mean HDL-c percentage change from baseline (%)					
All trials [43,139,144,145,153,154,165,170,177]	9	911	0.33	-1.86	2.52
Participants in need of intensive lipid lowering therapy [139,144,154,177]	4	367	2.25	-0.56	5.06
Participants with LDL>190 [139,144,177]	3	317	2.37	-1.18	5.93

Abbreviations: BAS = bile acid sequestrant, CI = 95% confidence interval, HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein cholesterol

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Table 34. Quantitative syntheses of short term harms and adherence data, for BAS plus statin therapy compared with statin monotherapy

	Number of trials reporting outcome	Number in relevant treatment groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Treatment adherence						
All trials[101,117,139,145,169]	5	1420	1262			
Simvastatin Lower dose statin in combination versus higher dose monotherapy[117]	1	81	64	0.33	0.09	1.27
Atorvastatin Lower dose statin in combination versus higher dose monotherapy[101]	1	39	35	0.94	0.12	7.48
At least one adverse event						
All trials[43,117,139,152]	4	522	301	2.19	1.28	3.75
All trials 24 weeks or more followup[43]	1	150	99	5.14	2.39	11.07
Simvastatin Lower dose statin in combination versus higher dose monotherapy[117]	1	83	44	1.19	0.47	3.02
Withdrawal due to adverse event						
All trials [43,101,139,145,152,165,170,177]	8	966	31	2.77	1.16	6.60
Atorvastatin Lower dose statin in combination versus higher dose monotherapy[101]	1	39	2	1.06	0.06	18.17
AST and/or ALT ≥ 3 times ULN, and/or hepatitis						
All trials [165,177]	2	212	0			
Myalgia						
All trials[99,139,153,165]	4	343	11	0.43	0.12	1.54
CPK ≥ 10 times the ULN						
All trials[139,177]	2	156	0			

Abbreviations: ALT = alanine transaminase, AST = aspartate transaminase, BAS = bile acid sequestrant, CI = 95% confidence interval, CPK = creatine phosphokinase

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Figure 52. Forest plot of all-cause mortality for BAS plus statin therapy compared with statin monotherapy, in all participants

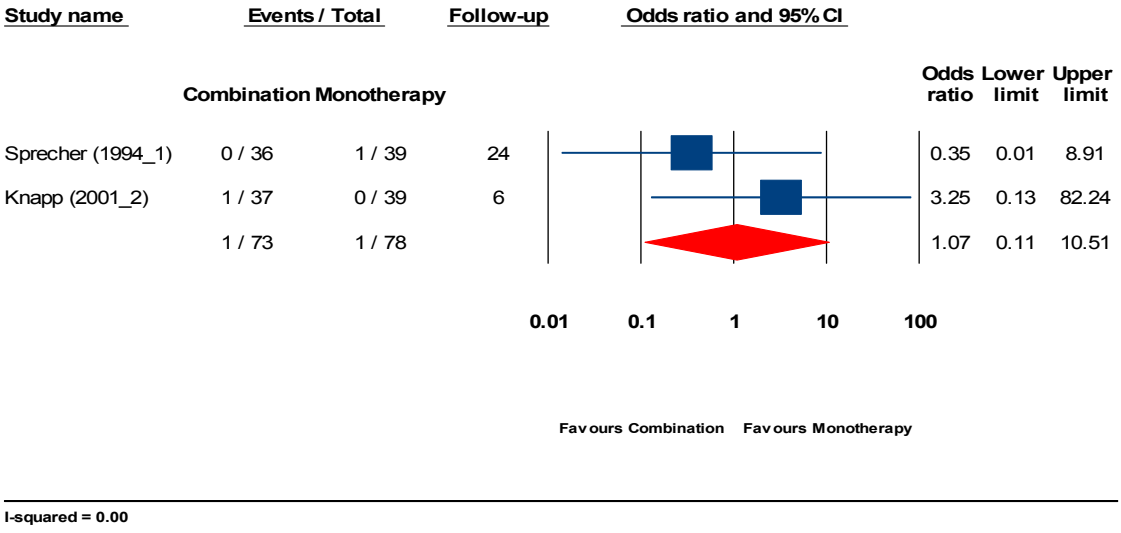


Figure 53. Forest plot of serious adverse events for BAS plus statin therapy compared with statin monotherapy, in all participants

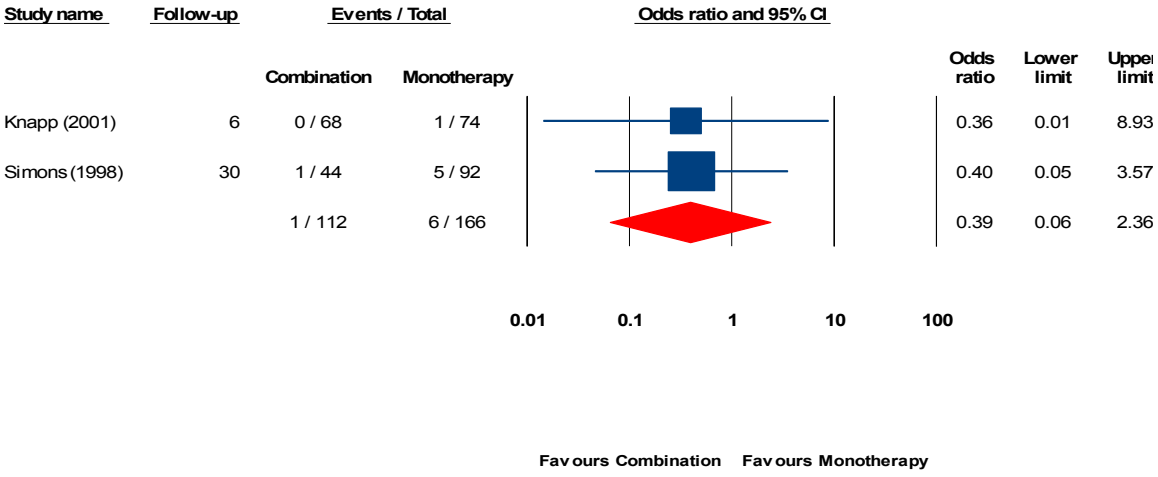
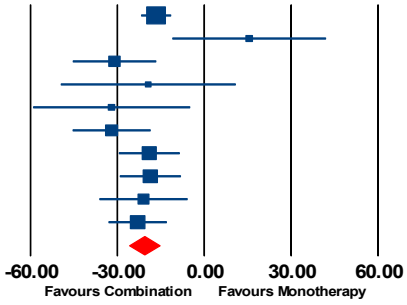


Figure 54. Forest and funnel plots of difference in LDL-c post-treatment means / mean change scores for BAS plus statin therapy compared with statin monotherapy, in all participants

Study name	Follow-up	Sample size		Difference in means and 95% CI			
		Combination	Monotherapy		Difference in means	Lower limit	Upper limit
Eriksson (1998)	96	270	406		-16.64	-21.89	-11.39
Isaacsohn (1997)	32	21	16		15.48	-11.14	42.10
PMSG II (1993)	16-24	61	57		-31.00	-45.48	-16.52
Heinonen (1996)	11	20	41		-19.35	-49.63	10.93
Ismail (1990)	8	9	17		-32.00	-59.20	-4.80
Knapp (2001_1)	6	34	35		-32.00	-45.52	-18.48
Knapp (2001_2)	6	37	39		-19.00	-29.60	-8.40
Davidson (2001)	4	50	26		-18.64	-29.27	-8.01
Hunninghake (2001)	4	18	18		-21.00	-36.31	-5.69
Schrott (1995)	4-12	23	24		-23.00	-33.17	-12.83
		543	679		-20.78	-26.02	-15.54



I-squared = 39.21

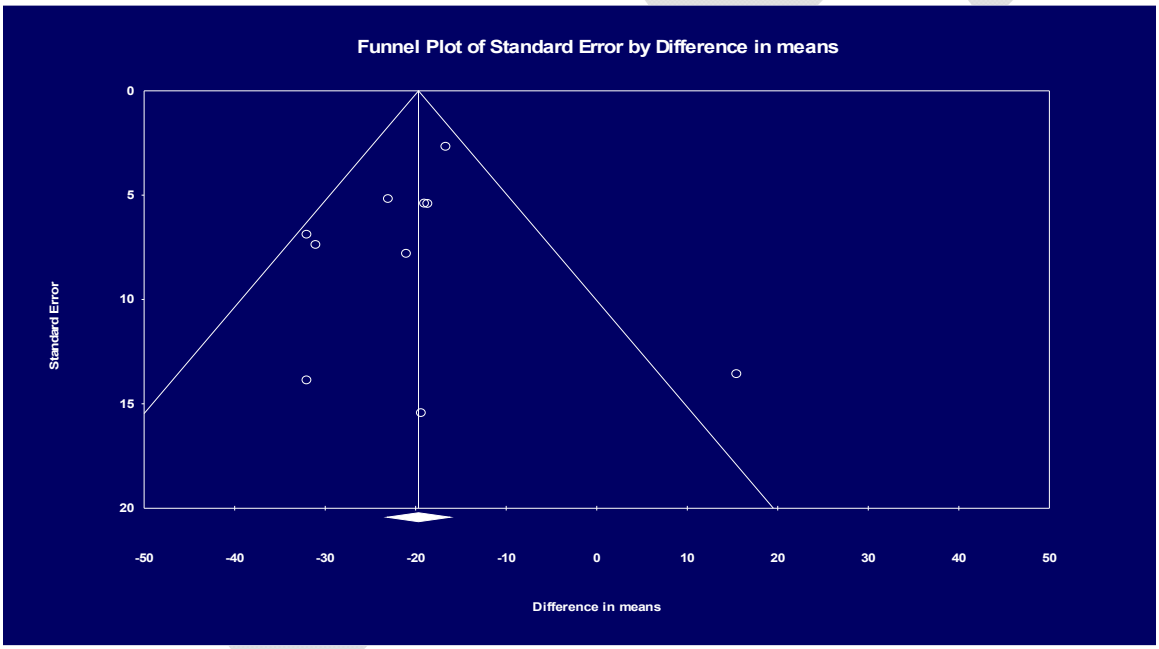
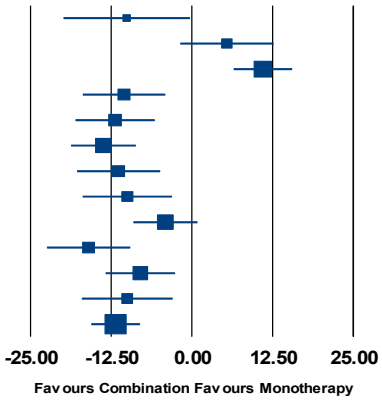
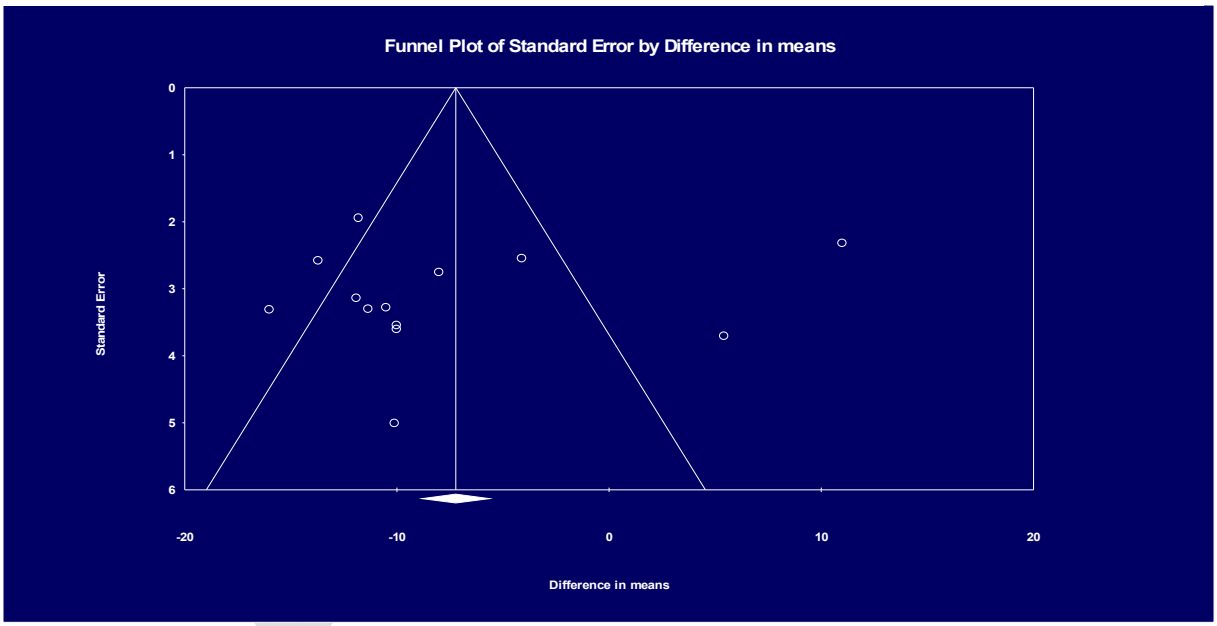


Figure 55. Forest and funnel plots with Egger's regression test, of difference in LDL-c mean percentage change from baseline, for BAS plus statin therapy compared with statin monotherapy in all participants

Study name	Follow-up	Sample size		Difference in means and 95% CI			
		Combination	Monotherapy		Difference in means	Lower limit	Upper limit
O'Brien (1990)	40	35	15		-10.10	-19.92	-0.28
Isaacsohn (1997)	32	21	16		5.43	-1.84	12.70
Simons (1998)	30	44	92		11.00	6.45	15.55
Sprecher (1994_1)	24	35	38		-10.50	-16.94	-4.06
Sprecher (1994_2)	24	35	38		-11.90	-18.06	-5.74
PMSG II (1993)	16-24	61	57		-13.70	-18.76	-8.64
Simons (1992)	12	39	22		-11.34	-17.82	-4.86
Heinonen (1996)	11	20	41		-10.00	-16.95	-3.05
Ballantyne (2004_a)	6	75	69		-4.10	-9.10	0.90
Knapp (2001_1)	6	34	35		-16.00	-22.50	-9.50
Knapp (2001_2)	6	37	39		-8.00	-13.40	-2.60
Hunninghake (2001)	4	18	18		-10.00	-17.07	-2.93
Davidson (2001)	4	50	26		-11.80	-15.62	-7.98



I-squared = 87.98

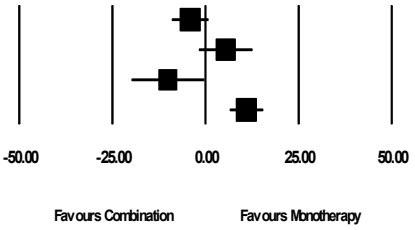


Egger's regression intercept

Intercept	-1.70221
Standard error	3.62381
95% lower limit (2-tailed)	-9.67816
95% upper limit (2-tailed)	6.27374
t-value	0.46973
df	11.00000
P-value (1-tailed)	0.32386
P-value (2-tailed)	0.64772

Figure 56. Forest plot of difference in LDL-c mean percentage change from baseline for BAS plus statin therapy compared with statin monotherapy, in participants requiring intensive lipid lowering therapy

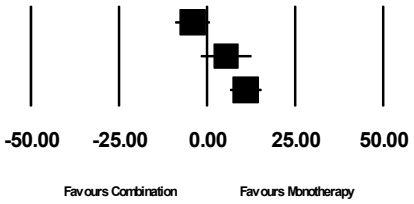
Followup	Studyname	Statistics for each study				Sample size	
		Difference in means	Standard error	Lower limit	Upper limit	Combination	Monotherapy
6	Ballantyne (2004_a)	-4.100	2.550	-9.098	0.898	75	69
32	Isaacsohn (1997)	5.430	3.709	-1.839	12.699	21	16
40	O'Brien (1990)	-10.100	5.010	-19.919	-0.281	35	15
30	Simons (1998)	11.000	2.323	6.446	15.554	44	92



Model: random effects **I-squared: 89%**

Figure 57. Forest plot of difference in LDL-c mean percentage change from baseline, for BAS plus statin therapy compared with statin monotherapy, in participants with LDL-c above 190 mg/dL

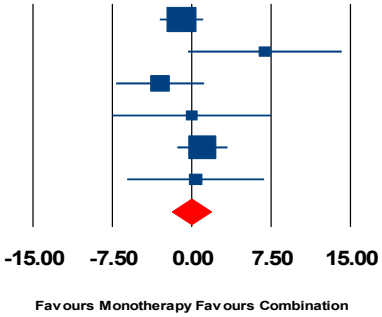
Followup	Study name	Statistics for each study			
		Difference in means	Standard error	Lower limit	Upper limit
6	Ballantyne (2004_a)	-4.100	2.550	-9.098	0.898
32	Isaacsohn (1997)	5.430	3.709	-1.839	12.699
30	Simons (1998)	11.000	2.323	6.446	15.554



Model: random effects **I-squared: 90%**

Figure 58. Forest and funnel plots of difference in HDL-c post-treatment means / mean change scores for BAS plus statin therapy compared with statin monotherapy, in all participants

Study name	Follow-up	Sample size		Difference in means	Lower limit	Upper limit
		Combination	Monotherapy			
Eriksson (1998)	96	272	827	-0.97	-3.03	1.09
Isaacsohn (1997)	32	21	16	6.90	-0.37	14.17
PMSG II (1993)	16-24	61	57	-3.00	-7.16	1.16
Heinonen (1996)	11	40	41	0.00	-7.49	7.49
Davidson (2001)	4	50	26	1.00	-1.39	3.39
Schrott (1995)	4-12	46	24	0.37	-6.12	6.86
		490	991	-0.05	-1.91	1.80



I-squared = 27.91

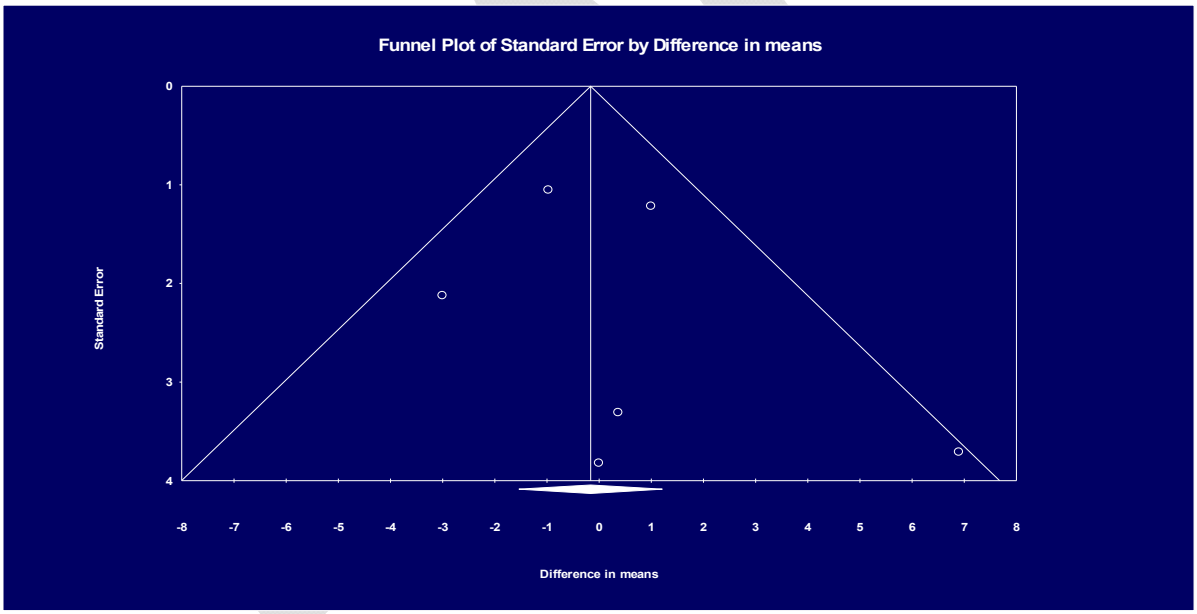
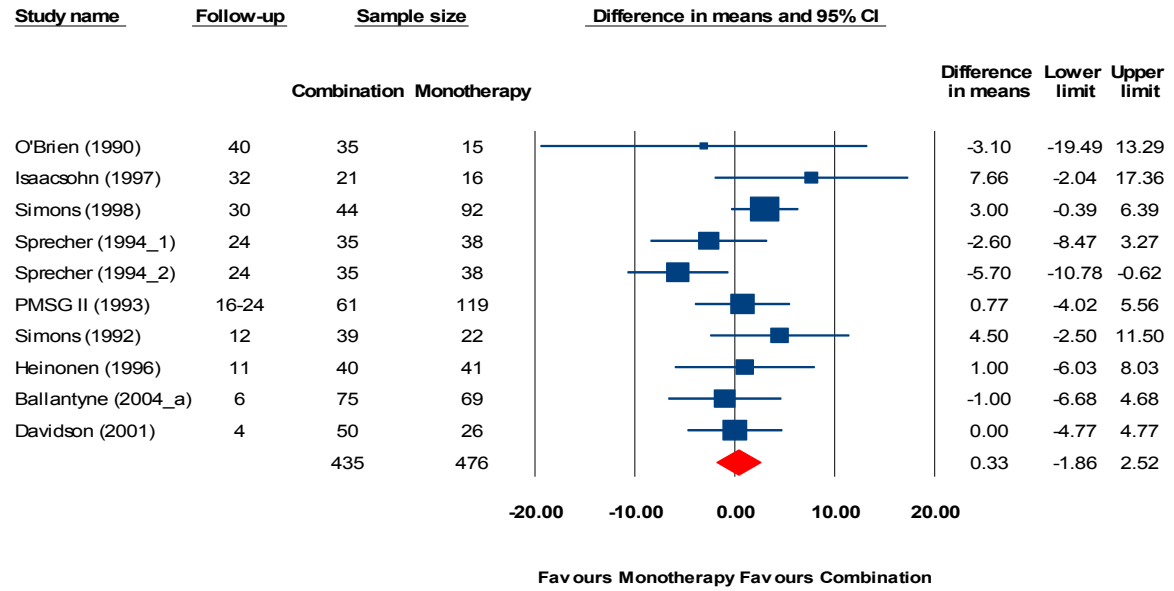


Figure 59. Forest and funnel plots of difference in HDL-c mean percentage change from baseline for BAS plus statin therapy compared with statin monotherapy, in all participants



I-squared = 29.44

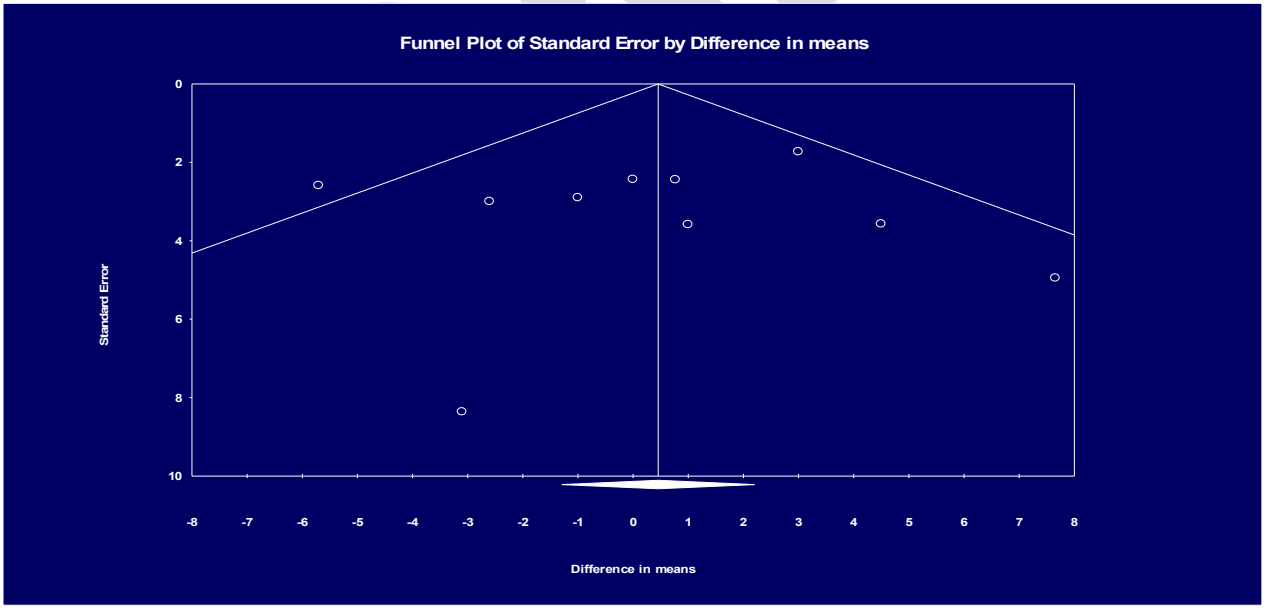
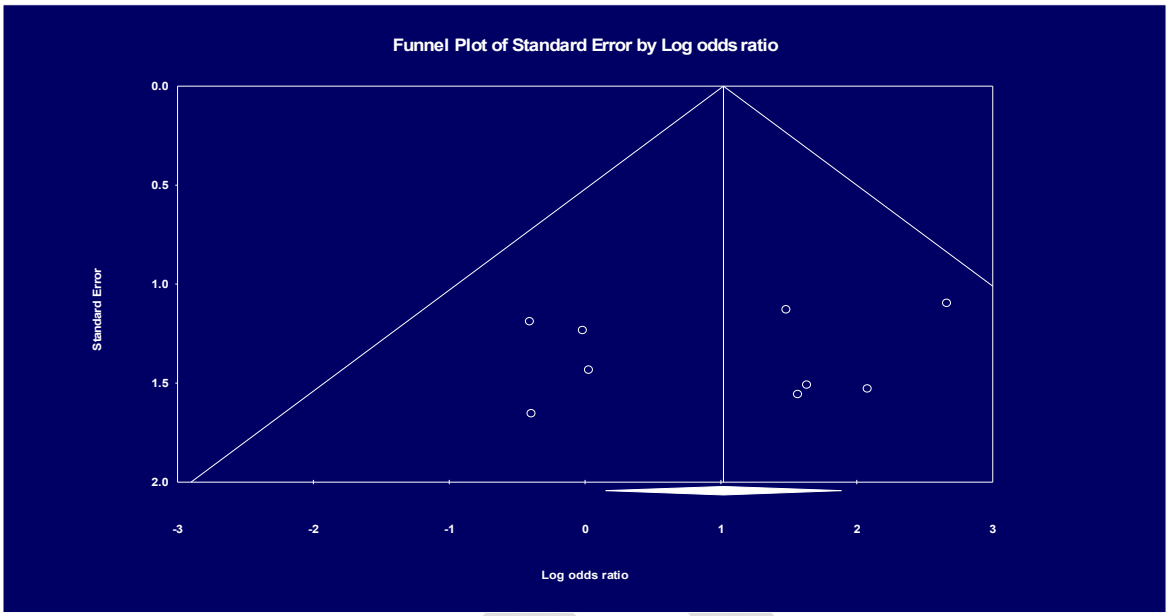


Figure 60. Funnel plot of participants withdrawing from treatment due to adverse events for BAS plus statin therapy compared with statin monotherapy, in all participants



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Omega-3 Fatty Acid Combination Therapy Versus Statin Monotherapy

Overview of included studies

A total of 10 randomized controlled trials trial reports evaluated relative efficacy and/or harms of the combination of statin plus Omega-3 compared with statin monotherapy, in a total of 19212 participants (Table 4, Appendix D). This should be noted that majority of participants were from one study.[124] None of the included non-randomized studies addressed this particular comparison. Four randomized trials had more than one associated journal published or FDA report (Table 6). None of the trials had any companion or extension report of longer treatment or followup period.

Two trials were conducted in multiple centers,[124,160] and eight trials in a single centre.[98,146,155-159,178]

Five of ten trials were partially or completely sponsored by the pharmaceutical industry,[98,124,156,157,160] while funding was not reported or unclear in five reports.[146,155,158,159,178]

Total Jadad score for trial reports ranged from one to four. Four trial reports demonstrated an appropriate method of randomization,[124,155,160,178] while six reported an appropriate method of double blinding.[98,146,155-157,160] Allocation concealment was reported as adequate in four trials.[124,155,160,178]

Distribution of trials by geographical region as follows:

- North America - 2 trials[158,160]
- Europe - 4 trials[146,156,157,159]
- Asia - 2 trials[124,155]
- Australia - 2 trials[98,178]

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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 co-administration of different lipid-modifying agents (i.e. a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

A total of four trials, randomizing 19002 participants, compared statin plus Omega-3 fatty acid combination therapy with statin monotherapy, and reported one or more of the clinical outcomes, serious adverse events or cancer (Table 35).[124,156,157,160] There were no trials exclusively in females.

Two trials included participants of Asian descent,[124,160] with one trial being exclusively in participants of Asian descent.[124] One trial included participants of Hispanic descent,[160] and one trial included participants of African descent.[160]

Among reports of trials including information on ethnicity, one reported a mean of 96% of participants to be of European descent; one reported a mean of 2% of African descent; two reported a mean of 51% of Asian descent (range 1-100%); and one reported a mean of 2% of Hispanic descent.

Trial duration ranged from 5 to 240 weeks with an average of 69 weeks. Although no trial totally excluded the female gender, on average 42% of participants were women (range 27% - 69%).

The average of mean ages of participants was 56 years (range 47 - 61 years).

Three of the trials recruited outpatients,[156,157,160] while one trial did not report recruitment setting.

The mean Jadad score for trial reports was 3.25 (range: 2 - 4), and two trials reports reported an adequate method of allocation concealment.[124,160]

Of the 4 trials, only one trial was exclusively in participants requiring intensive lipid lowering treatment (i.e. participants with established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL).[156]

Outcomes with no available Evidence

No trials compared lower dose statin plus omega-3 with higher dose of statin monotherapy. Furthermore, no analyzable data was available regarding patients with vascular death, cerebrovascular events, transient ischemic attacks, acute coronary syndrome, carotid endarterectomy, percutaneous coronary intervention, coronary arterial bypass graft, unspecified revascularization procedures, and/or serious adverse events.

Participants with all-cause mortality: Omega-3 - statin combination versus statin monotherapy

All-cause data was reported for three trials,[124,157,160] two of which presented an adequate form of allocation concealment,[124,160] and one trial which had a followup of 24 weeks or more (Table 35).[124] Of these trials, only one trial presented analyzable data.[124] This trial report demonstrated that there was no statistically significant difference in the incidence of mortality between the

Omega-3 plus statin combination compared with statin monotherapy (OR = 1.08; 95% CI 0.91, 1.28) based 551 deaths.

Participants with myocardial infarction: Omega-3 - statin combination versus statin monotherapy

Incidence of myocardial infarction as well as non-fatal myocardial infarction was reported for one trial,[124] which had a followup duration of 240 weeks (Table 35). Fatal myocardial infarction was reported for two trials, both of which had a followup duration of 24 weeks or more (range: 24 - 240 weeks).[124,156]

Myocardial infarction data from one trial demonstrated no significant difference between the Omega-3 plus statin combination compared with statin monotherapy (OR = 0.76; 95% CI 0.56, 1.04) based upon 164 events.[124] Non-fatal myocardial infarction data from the same trial demonstrated no statistically significant difference in the incidence of non-fatal myocardial infarction between the Omega-3 plus statin combination compared with statin monotherapy (OR = 0.74; 95% CI 0.54, 1.04), based upon 145 events.[124]

Pooling of fatal myocardial infarction data from two trials demonstrated no statistically significant difference in the incidence of fatal myocardial infarction between the Omega-3 plus statin combination compared with statin monotherapy (OR = 0.74; 95% CI 0.34, 1.60).[124,156]

Participants with stroke: Omega-3 - statin combination versus statin monotherapy

Stroke, hemorrhagic stroke and ischemic stroke, were reported for one trial, which had a followup duration of 240 weeks follow-up (Table 35).[124] There was no significant difference in the incidence of participants with stroke (e.g. hemorrhagic or ischemic) between the Omega-3 plus statin combination compared with statin monotherapy (OR = 1.02; 95% CI 0.82, 1.27), based upon 328 participants experiencing stroke. This incidence was similar for participants with hemorrhagic stroke (OR = 1.26; 95% CI 0.82, 1.92) and ischemic stroke (OR = 0.93; 95% CI 0.72, 1.21).

Participants with cancer: Omega-3 - statin combination versus statin monotherapy

Cancer data was reported for one trial (Table 35).[124] This data demonstrated that there was no significant difference in the incidence of patients developing cancer (OR = 1.11; 95% CI 0.92, 1.34) based upon 460 cases.

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Key Question 2: Do these regimens differ in reaching LDL-targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

A total of ten trials yielded data on participants reaching LDL-c targets and/or other surrogate markers of efficacy, short-term side effects, tolerability, and/or treatment adherence (Table 36-39).[98,124,146,155-160,178]

Two trials included participants of Asian descent,[124,160] with one trial being exclusively in participants of Asian descent.[124] One trial included participants of Hispanic descent,[160] and one trial included participants of African descent.[160]

There were no trials exclusively in females, or participants of Hispanic, and/or African descent.

Reporting of participants' ethnic background was as follows:

- European descent: 1 trial, mean 96%
- Asian descent: 2 trials, mean 51% (range, 1%-100%)
- Hispanic descent: 1 trial, mean 2%
- African descent: 1 trial, mean 2%

Trial duration ranged from 5 – 240 wks with an average of 34 weeks. Only one trial totally excluded the female gender, and on average 39% of participants were women (range: 0 – 78 %). The average of mean ages of participants was 56 years (range: 47 – 61 years). Seven of the trials recruited outpatients,[98,146,155-157,160,178] while three trials did not report recruitment setting.[124,158,159] Mean Jadad score was 3.00 (range: 2 – 4) and four trials had adequate allocation concealment.[124,155,160,178]

Of these ten trials, only two were exclusively in participants requiring intensive lipid lowering treatment (i.e. participants with established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL).[155,156]

Outcomes with no available evidence

No data was available regarding the following outcomes: number of patients attaining ATP-III LDL-c targets; carotid plaque area, plaque volume, measure of stenois, and/or calcification; coronary plaque area, plaque volume, measure of stenois or calcification; treatment adherence; elevated serum AST and/or ALT above 3 times the upper limit of normal and/or hepatitis; and myalgia.

Surrogate outcomes

LDL-c: Omega-3 - statin combination versus statin monotherapy

The surrogate outcome LDL-c was reported for eight trials (Table 36). All presented data for post-treatment means/ change score[98,146,155-157,159,160,178] in 553 participants and two[98,160] additionally presented data for the percentage change from baseline in 278 participants. Pooling demonstrated no significant differences between the Omega-3 plus statin combination compared with statin monotherapy in the LDL-c post-treatment means/ change score (MD = 0.96 mg/dL; 95% CI -5.75 mg/dL, 7.68 mg/dL) (Figure 61). These results were in contrast to the difference mean percentage change from baseline, which demonstrated a significantly greater decrease in

LDL-c concentrations following statin monotherapy (MD = 5.26; 95% CI 1.79%, 8.74%) (Figure 63).

HDL-c: Omega-3 - statin combination versus statin monotherapy

The surrogate outcome HDL-c was reported for nine trials as post-treatment means/ change score,[98,146,155-160,178] and additionally as percentage change from baseline for three trials (Table 37).[98,158,160] For the post-treatment means/ change score, data was heterogeneous and therefore pooling of the data was not performed (I^2 = 64.85%) (Figure 64). The trials had varying followup periods, ranging from 5 to 24 weeks, and varying inclusion/ exclusion criteria.

For HDL-c percentage change from baseline, data was homogenous and meta-analysis demonstrated a significantly higher HDL-c increase with statin combination therapy with Omega-3 plus statin combination than statin monotherapy (MD = 5.31%; 95% CI 3.16%, 7.45%).

TC:HDL-c ratio: Omega-3 - statin combination versus statin monotherapy

Three reports presented data for post-treatment means/ change score[155,158,160] and additionally two as percentage change from baseline (Table 38).[158,160] For post-treatment means/ change score, meta-analysis demonstrated no statistically significant difference between the two groups (MD = -0.41; 95% CI -0.88, 0.06). These results were in contrast to the percentage change from baseline which demonstrated a significantly greater decrease in TC:HDL-c concentrations following Omega-3 plus statin combination therapy compared with statin monotherapy (MD = -7.77%; 95% CI -10.27%, -5.27%).

Treatment adherence and harms

Participants with an adverse event: Omega-3 - statin combination versus statin monotherapy

Total adverse events was reported for six trials,[124,146,156,157,159,160] three of which presented analyzable data (Table 39).[124,156,160] Meta-analysis demonstrated no significant difference in the incidence of patients with adverse events in either group (OR = 1.11; 95% CI 0.82, 1.51). Two trials had a followup duration of 24 weeks or more (range: 24 - 240 weeks).[124,156] Pooling of the data from these trials demonstrated a significant higher incidence with Omega-3 plus statin combination compared with statin monotherapy (OR = 1.22; 95% CI 1.44, 1.31) based upon 4377 participants with events.

Participants withdrawing due to adverse events: Omega-3 - statin combination versus statin monotherapy

Withdrawal due to adverse events was reported for one trial (Table 39).[160] This data demonstrated no significant difference in the incidence of participants who withdrew due to adverse events following Omega-3 plus statin combination therapy compared with statin monotherapy, based on six events/participants (OR = 1.09; 95% CI 0.22, 5.52).

Participants with rhabdomyolysis: Omega-3 - statin combination versus statin monotherapy

The number of participants with rhabdomyolysis was reported for one trial, with no events in either arm (Table 39).[160]

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Participants with CPK above 10 times the upper limit of normal: Omega-3 - statin combination versus statin monotherapy

The number of participants with CPK above10 times the upper limit of normal was reported for three trials, with no events in any treatment arm (Table 39).[146,157,160]

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Key Question 3: Compared with higher-dose statins, and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

Longer term outcomes

All-cause mortality: Omega-3 - statin combination versus statin monotherapy

Most trials included primarily participants of European origin, but other racial characteristics of the included population were addressed by one trial.

Participants of Asian descent. One trial presented data regarding all-cause mortality within a subgroup of persons of Asian descent[124]. The trial utilized an adequate form of allocation concealment had a followup of 240 weeks or more. For this trial there was no statistically significant difference in the incidence of mortality between the participants on Omega-3 plus statin combination compared with statin monotherapy (OR = 1.08; 95% CI 0.91, 1.28) based 551 deaths.

Participants requiring intensive lipid lowering therapy. Two trials provided data for participants requiring intensive lipid lowering treatment (i.e. participants with established vascular disease and/or diabetes mellitus and/or baseline LDL-c above 190 mg/dL).[155,156] Of these trials, one was on participants with established vascular disease.[156]

Further, no trial reports presented data for any of the other subgroups of interest to this review.

Surrogate outcomes

LDL-c: Omega-3 - statin combination versus statin monotherapy

Participants requiring intensive lipid lowering therapy. Two trials reported LDL-c post-treatment means/ change score.[155,156] Both trials demonstrated a greater reduction in LDL-c with the Omega-3 plus statin combination compared with statin monotherapy, but the degree of reduction was heterogeneous so pooling was not performed (I^2 = 81%). Generally participants on prior statin therapy who had persisting hypertriglyceridaemia[156] experienced a greater reduction than participants who were statin naïve.[155] In addition, the latter group had a higher baseline LDL-c (149 mg/dL compared with 90 mg/dL), that may have contributed to the greater reduction in post-treatment values.

LDL-c: Omega-3 - statin combination versus statin monotherapy

Participants with established vascular diseases. For the surrogate outcome 'LDL-c in participants with established vascular diseases', data was provided from one trial report, which presented data for post-treatment means/ change score.[156] The trial report demonstrated a significant reduction in LDL-c with the Omega-3 plus statin combination compared with statin monotherapy (MD = -42.57 mg/dL; 95% CI -72.43 mg/dL, -12.71 mg/dL).

HDL-c: Omega-3 - statin combination versus statin monotherapy

Participants requiring intensive lipid lowering therapy. HDL-c post-treatment means/ change score was reported for two trials.[155,156] Data was heterogeneous and therefore pooling of the data

was not performed (I^2 = 85%). Participants on prior statin therapy who had persisting hypertriglyceridaemia experienced a reduction in HDL-c means,[156] while participants who were statin naïve experienced a minor increase.[202]

Participants with established vascular diseases. HDL-c post-treatment means/ change score was reported for two trials,[155,156] with a pooled significant reduction in LDL-c for the Omega-3 plus statin combination compared with statin monotherapy (MD = -11.61 mg/dL; 95% CI -18.80 mg/dL, -4.42 mg/dL).

TC:HDL-c ratio: Omega-3 - statin combination versus statin monotherapy

Participants requiring intensive lipid lowering therapy. TC:HDL-c ratio post-treatment means/ change score were reported for one trial.[155] There was no statistically significant difference between the Omega-3 plus statin combination compared with statin monotherapy (MD = -0.37; 95% CI -1.43, 0.61).

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Tables and Figures: Omega-3 Fatty Acid - Statin Combination Therapy versus Statin Monotherapy

Table 35. Quantitative syntheses of longer term outcomes data (clinical, serious adverse events and cancer) for Omega-3 plus statin therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant intervention groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
All-cause mortality						
All trials[124,160,203]	3	18940	551	1.08	0.91	1.28
All trials 24 weeks or more followup[124]	1	18645	551	1.08	0.91	1.28
Adequate allocation concealment[124,160]	2	18899	551	1.08	0.91	1.28
Participants of Asian descent[124]	1	18645	551	1.08	0.91	1.28
Myocardial infarction						
Fatal myocardial infarction[124,156]	2	18700	26	0.74	0.34	1.6
Non-fatal myocardial infarction[124]	1	18645	145	0.74	0.54	1.04
Any myocardial infarction[124]	1	18645	164	0.76	0.56	1.04
Stroke						
Hemorrhagic stroke[124]	1	18645	88	1.26	0.82	1.92
Ischemic stroke[124]	1	18645	238	0.93	0.72	1.21
Any stroke[124]	1	18645	328	1.02	0.82	1.27
Serious adverse events						
Serious adverse events[160]	1	254	5	4.44	0.49	40.29
Cancer						
Cancer[124]	1	18645	460	1.11	0.92	1.34

Abbreviations: CI 95% confidence interval

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Table 36. Quantitative syntheses of LDL-c data for Omega-3 plus statin therapy compared with statin monotherapy

	Number of trials reporting outcome	Number of participants in relevant intervention groups	Point Estimate	Lower CI	Upper CI
Difference in means - change from baseline LDL-c (mg/dL)					
All trials, all participants[98,155-157,159,160,178,204]	8	533	-0.58	-7.25	6.09
Participants requiring intensive lipid lowering therapy [155,156]	2	95			
Participants with vascular disease[156]	1	55	-42.57	-72.43	-12.71
Difference in mean percentage change from baseline (%)					
All trials[98,160]	2	278	5.26	1.79	8.74

Abbreviations: CI 95% confidence interval, HDL-c = high density lipoprotein cholesterol

Table 37. Quantitative syntheses of HDL-c data for Omega-3 plus statin therapy compared with statin monotherapy

Population	Number of trials reporting outcome	Number of participants in relevant intervention groups	Point Estimate	Lower CI	Upper CI
Difference in means - change from baseline HDL-c (mg/dL)					
All trials[98,146,155-160,178]	9	557	-	-	-
Difference in means - change from baseline HDL-c (mg/dL) (High-risk population)					
All trials[155,156]	2	95	-	-	-
Difference in means - change from baseline HDL-c (mg/dL) (Population with vascular disease)					
All trials[156]	1	55	-11.61	-18.80	-4.42
Difference in mean percentage change from baseline (%)					
All trials[98,158,160]	3	297	5.31	3.16	7.45

Abbreviations: CI 95% confidence interval, HDL-c = high density lipoprotein cholesterol

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Table 38. Quantitative syntheses of total cholesterol : HDL-c ratios for Omega-3 plus statin therapy compared with statin monotherapy

Outcome	Number of trials reporting outcome	Number of participants in relevant intervention groups	Odds ratio	Lower CI	Upper CI
Difference in changes in mean TC:HDL-c					
All trials[155,158,160]	3	313	-0.41	-0.88	0.06
Difference in changes in mean TC: HDL-c in participants requiring intensive lipid lowering therapy					
All trials[155]	1	40	-0.37	-1.43	0.61
Difference in changes in mean TC:HDL-c					
All trials[158,160]	2	273	-7.77	-10.27	-5.27

Abbreviations: CI 95% confidence interval, TC = total cholesterol, HDL-c = high density lipoprotein cholesterol

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Table 39. Quantitative syntheses of short term harms and adherence for Omega-3 plus statin therapy compared with statin monotherapy

Outcome	Number of trials reporting outcome	Max dose omega-3	Number of participants in relevant intervention groups	Number of participants with events	Odds ratio	Lower CI	Upper CI
Relative probability of an adverse event							
All trials[124,146,156,157,159,160]	6	1800 – 9200	19074	4491	1.11	0.82	1.51
Trials 24 weeks or longer[124,156]	2	1800 - 4000	18700	4377	1.22	1.14	1.31
Relative probability of participants withdrawing from treatment due to an adverse event							
All trials[160]	1	4000	255	6	1.09	0.22	5.52
Relative probability of participants experiencing elevated serum AST and/or ALT > 3 times the upper limit of normal and/or hepatitis							
All trials[146,157,160]	3	2000 - 4000	337	0			
Relative probability of participants experiencing CPK greater than 10 times the upper limit of normal							
All trials[146,157,160]	3	2000 - 4000	337	0			
Relative probability of participants experiencing rhabdomyolysis (investigator defined)							
All trials[160]	1	4000	254	0			

Abbreviations: ALT = alanine transaminase, AST = aspartate transaminase, CI = 95% confidence interval, CPK = creatine phosphokinase

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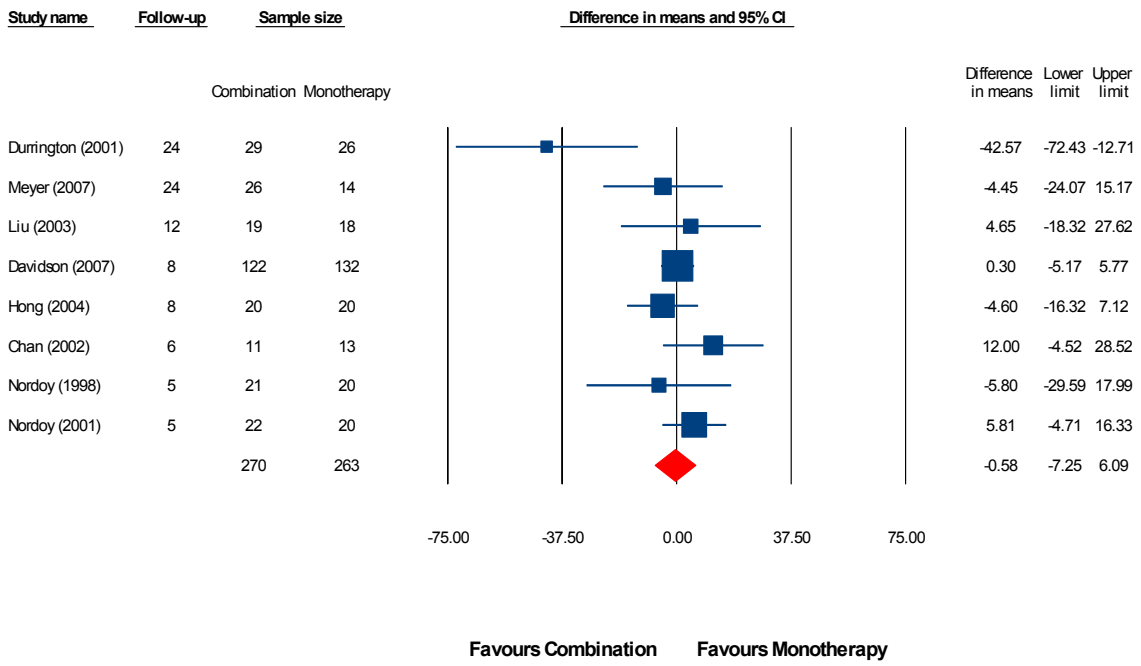
Figure 61. Forest and funnel plots of difference in LDL-c post-treatment means / mean change scores for omega-3 fatty acid plus statin therapy compared with statin monotherapy, in all participants



I-squared = 42.56

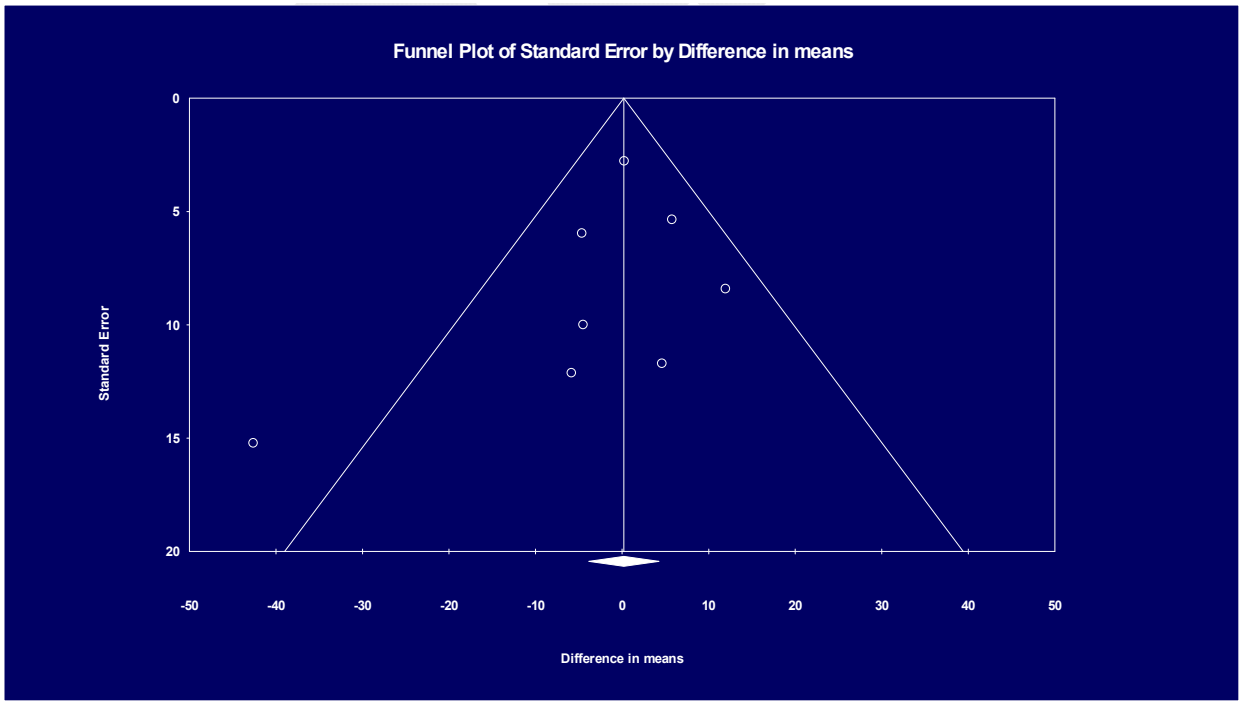
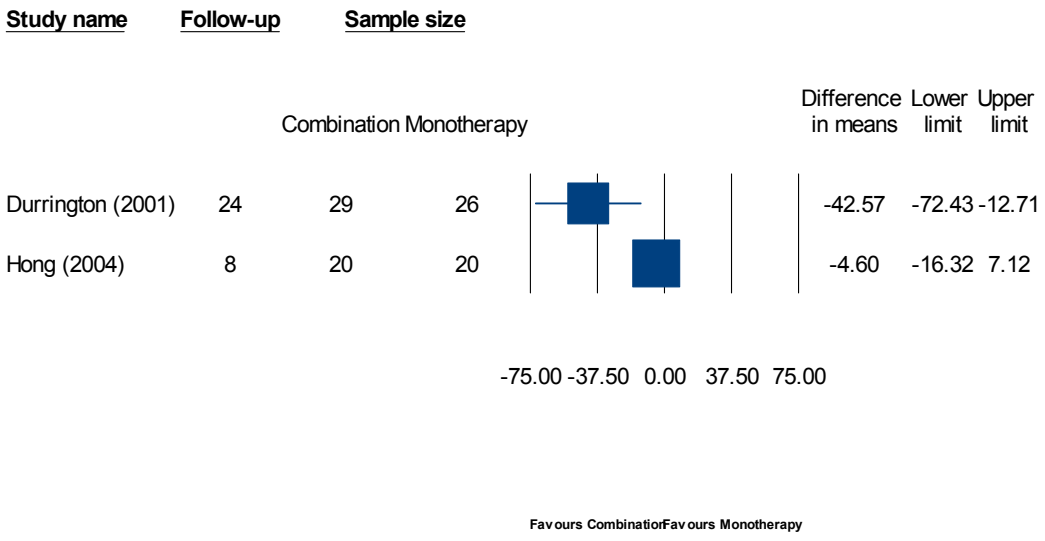


Figure 62. Forest plot of difference in LDL-c post-treatment means / mean change scores for omega-3 fatty acid plus statin therapy compared with statin monotherapy, in participants requiring intensive lipid lowering therapy



I-squared = 81.43

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Figure 63. Forest plot of difference in LDL-c mean percentage change from baseline for omega-3 fatty acid plus statin therapy compared with statin monotherapy, in all participants

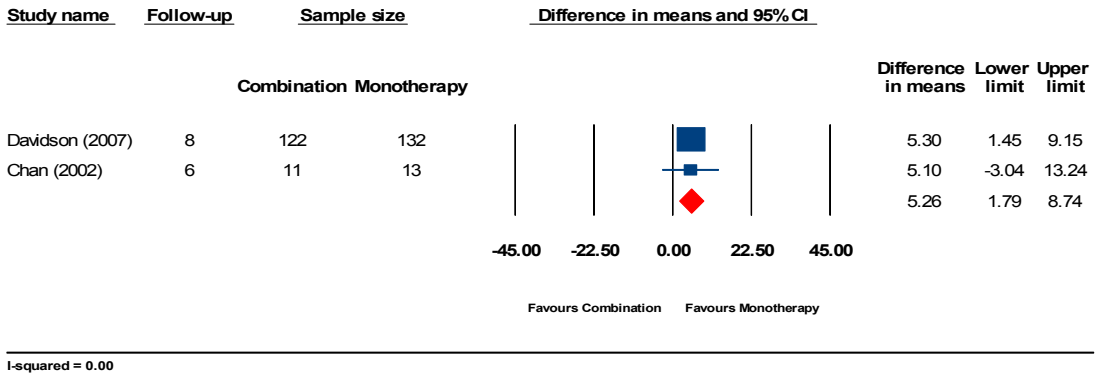

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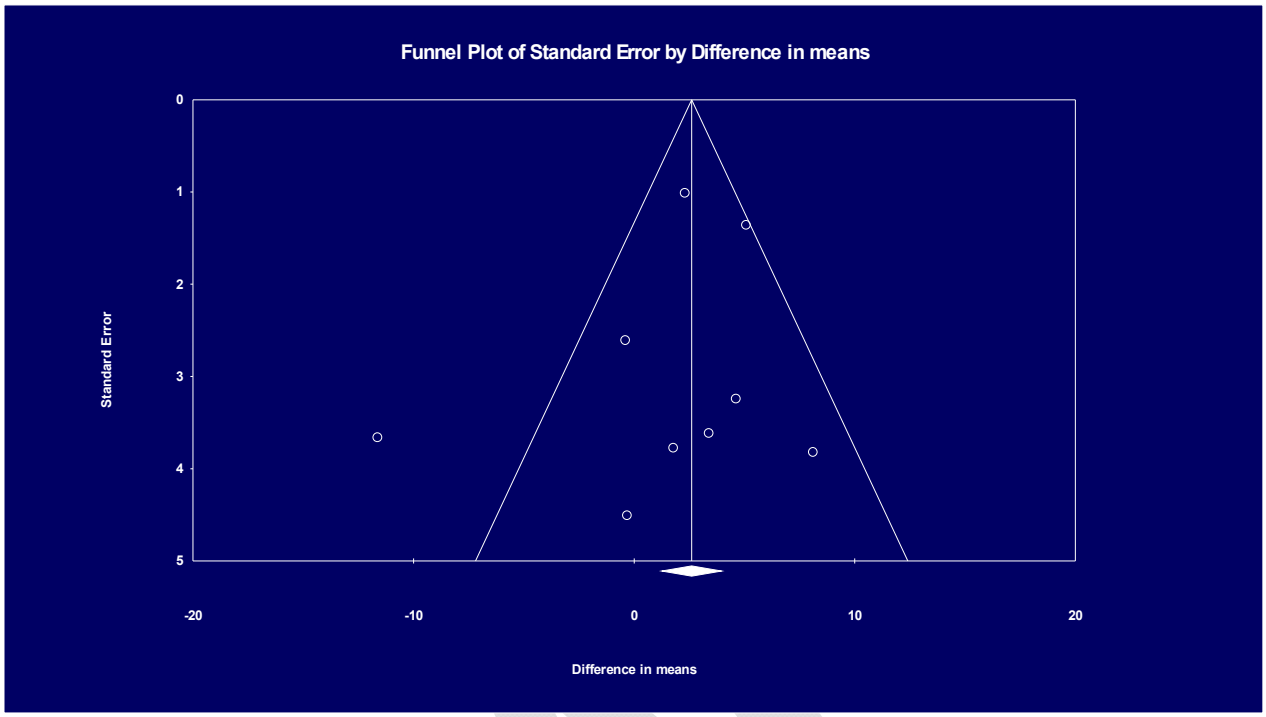
Figure 64. Funnel plot of difference in HDL-c mean percentage change from baseline for omega-3 fatty acid plus statin therapy compared with statin monotherapy, in all participants



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Summary and Discussion

Strength of Evidence

The strength of the available evidence was assessed as GRADE (Grading of Recommendations Assessment, Development and Evaluation) [205] for the key outcomes all-cause mortality, vascular death, serious adverse events and achieving ATP-III target LDL-c using GRADEpro. Summary results are presented in Tables 40 to 56, and full reports are presented in Appendix D. GRADE was "low" to "very low," with the exception of moderate evidence that omega-3 plus statin combination therapy is associated with the same odds ratio for all-cause mortality as statin monotherapy. Our evaluation of the strength and applicability of evidence for these most important outcomes in the medication combinations studied is summarized according to the key questions in Table 57.

Discussion

This report addresses the effectiveness and safety of lipid modifying agents added to statin therapy. As expected, few long term studies were available reporting on major clinical endpoints such as incidence of myocardial infarction, mortality, adverse events and adherence. Most of the available evidence focused on short term studies of surrogate markers linked to vascular disease. The largest number of trials were found for the ezetimibe plus statin combination, with fewer studies for other combinations.

A clinical decision of interest, in the face of continued dyslipidemia, is whether to increase the dose of statin monotherapy or to add another medication. However, the comparator for most trials was not a higher, but rather the same dose of statin monotherapy. Indeed, a number of publications specifically stated that the comparator was the starting dose of the particular statin. Of note, a recent meta-analysis comparing more intensive statin treatment with less intensive treatment demonstrated a significant reduction in LDL-c levels in high risk patients with more intensive therapy. No statistical difference was observed in discontinuation rates attributable to drug related harms.[206] Further, as discussed below, multiple medications may decrease adherence to treatment, a critical factor in determining the outcomes of individuals on long term preventive therapies.

A single included study compared statin combination therapies using niacin or ezetimibe, with statin monotherapy.[122] All treatments examined resulted in similar reductions in LDL-c, while the niacin combination therapy resulted in significantly greater increases in HDL-c. No other direct comparisons of various combinations were identified, so the effect of these strategies can only be compared indirectly.

Clinical outcomes

All cause mortality and vascular death in individuals requiring intensive lipid lowering therapy was not specifically examined in trials of combination therapy and higher dose monotherapy, so was not observed to differ between treatment groups for any of the combinations studied.

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We therefore examined all trials providing evaluable data on these endpoints, irrespective of statin dose, and found a neutral odds ratio for all-cause mortality with ezetimibe, bile acid sequestrants, fibrate, niacin, or omega-3 fatty acids in combination with statins, compared with statin monotherapy. It should be noted that there were a small absolute number of deaths in the included trials, which is likely a function of the relatively short periods of followup. Thus the statistical power to observe such differences was low. This finding is in keeping with that of Josan et al, who noted a neutral impact on all-cause mortality with intensive statin therapy compared with lower dose statin therapy, in a quantitative systematic review of seven trials.[206] Similar findings were noted for vascular mortality. All reports of this outcome were restricted to a small absolute number of fatal myocardial infarctions, with no observed differences between combination and monotherapy treatments. A previous meta-analysis of mortality comparing classes of lipid modifying therapy to placebo suggested benefits from all therapies considered in the present review with the exception of fibrates, which were associated with an excess of noncardiovascular mortality.[207] A subsequent report suggested that this association disappears if trials employing clofibrate are excluded from statistical pooling.[208] Clofibrate is not approved for use in the US.

No significant difference was noted in the occurrence of nonfatal myocardial infarction or acute coronary syndrome. Indeed, there was no evidence of additional benefit from combination therapy when compared to a higher dose statin for any clinical outcomes. Several caveats are important to note regarding clinical outcomes. First, as noted above, most of the evidence to date has focused on short duration studies aimed at intermediate outcomes and there is insufficient data for most outcomes of clinical importance. Second, the comparator arms rarely explored higher doses of statin which may have advantages in terms of medication adherence and cost. While some data exists for the benefit of niacin and sequestrants alone or in combination with a statin in coronary heart disease, it remains unclear if the marginal benefit of adding these agents to a lower dose of a statin is a better strategy than increasing statin dose, particularly for individuals managed today.[34]

Stroke was a very rare event in this group of trials and no conclusions can be drawn regarding the differential impact of these interventions on its occurrence. While stroke is commonly considered an indication for lipid modification, note should be made that the NCEP ATP III guidelines specify symptomatic carotid disease as a coronary heart disease risk equivalent. This therefore excludes cardioembolic stroke, stroke due to small vessel disease and intracerebral hemorrhage as guideline supported indications for therapy. Ample evidence supports the beneficial effects of statins on stroke incidence in individuals with cardiac disease, but there is only a single trial in individuals treated after stroke.[12,209] In addition, lower cholesterol levels are associated epidemiologically with higher rates of intracranial hemorrhage, and statin treatment may increase the likelihood of its occurrence.[210,211] The therapeutic window for individuals treated after stroke may be narrower than for those with coronary heart disease. Further work is required to identify the characteristics of individuals with stroke whose potential for benefit with intensive lipid lowering exceeds any potential for harm. Trials are required with significant recruitment from secondary prevention stroke populations.

Serious Adverse Events

Our review of serious adverse events and cancer was not constrained to specific statin dose comparisons but rather included all trials comparing combination therapy with statin

monotherapy. The ezetimibe combination had the largest number of trials reporting this outcome, but the majority of these were less than 24 weeks duration, with a small minority reporting up to 52 weeks. In these longer duration studies the serious adverse events rate was approximately 10% for the combination and monotherapy groups, with no significant difference in proportions of participants experiencing serious adverse events between groups. One large trial of omega-3 fatty acids added to statin therapy in a Japanese population did not demonstrate any increase in cancer compared to monotherapy.[124] Data for the other interventions was sparse or had significant limitations.

Surrogate Outcomes

Ample evidence supports the selection of LDL-c as the primary target for lipid modifying therapy. A number of studies have established the correlation of LDL-c cholesterol and incident coronary heart disease or recurrent myocardial infarction in men and women.[212-217] Law, in a review of 164 trials of statins noted that these interventions reduce LDL-c by an average of 70 mg/dL, with a range from 70 to 108 mg/dL. For each reduction of 40 mg/dL cardiac events were reduced by 11% in the first year, 24% in the second and over 30 % subsequently.[218] More intensive statin therapy is associated with an reduced incidence of major cardiovascular events when compared to less intensive treatment.[206]

When compared to a higher dose of statin, no significant difference was found in LDL-c reduction for fibrate and bile acid sequestrants in populations requiring intensive lipid lowering. However, in two trials, one for each agent, significantly larger mean percentage reduction in LDL-c was demonstrated in participants with type 2 diabetes mellitus using combinations that included fibrate or bile acid sequestrants, compared with statin monotherapy. There were no trials with this comparison for the niacin and omega-3 combinations.

Overall, there was at best scant evidence to support a greater lowering of LDL-c with any of the five combinations reviewed over higher dose statin therapy. When combinations were compared to equal dose statin monotherapy, ezetimibe, niacin and BAS all produced additional reductions in LDL-c. The magnitude of the effect was greater for ezetimibe acknowledging the limitations of indirect comparisons. In all trials exceeding 6 weeks in duration of ezetimibe added to a statin in populations requiring intensive lipid lowering, the combination therapy was associated with an increased reduction in LDL-c ranging from 13 to 72 mg/dL. This compares to a pooled difference in the BAS trials of 20 mg/dL (26-16 mg/dL) and a reduction of 1 to 11mg/dL for niacin. Pooled results for fibrate and omega-3 fatty acids did not show a significant reduction in LDL-c compared with monotherapy. These findings are in keeping with our understanding of these agents. Both BAS and ezetimibe interfere with absorption from the intestines and would be expected to have an impact on LDL-c levels. When used as monotherapy, BAS decreases LDL-c by 15-30 %[34,219] and ezetimibe by 18 %,[220] while the reduction in LDL-c by fibrate has been considered marginal.[221]

Evidence was reviewed for the outcome of attainment of ATP III LDL-c goals for combination therapy compared to a higher dose statin. Ezetimibe in combination with simvastatin compared to higher dose simvastatin was associated with a significantly greater odds of attaining the LDL-c target (OR, 3.55, 95% CI 2.18 – 5.79) on the basis of two pooled trials. No difference was noted for fibrate on the basis of a single small trial, and no evidence was available for niacin, BAS or omega 3 combinations. As treatment to a target LDL-c is both the

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major goal of therapy as well as a justification for using combinations, this represents an important issue to be addressed in future work.

HDL-c is identified in the ATP III report as inversely correlated with coronary heart disease risk, and while the relationship is continuous, a level below 40 mg/dL has been identified as low.[34] A target for therapeutic intervention has not been set by these guidelines and it remains unclear whether raising HDL-c has an impact on coronary heart disease that is independent of LDL-c levels. For the direct comparison of combination therapy versus higher dose statin monotherapy, a single trial suggested no difference for combinations with ezetimibe or fibrate. In another trial, a significant increase in mean percentage change was noted for the combination of rosuvastatin 10 mg plus niacin 2 g compared with rosuvastatin 40 mg monotherapy in high risk individuals with low HDL-c (< 35 mg/dL). Niacin has an effect on HDL-c levels at low doses, while higher doses are required to reduce LDL-c.[34] Thus these findings are consistent with previous work on this agent.[175]

Some evidence suggests that treatment with niacin plus a statin may affect the progression of intermediate markers of atherosclerosis. Taylor examined the progression of CIMT in individuals with CAD and HDL-c below 45 mg/dL, treated with niacin or placebo added to ongoing statin therapy. Over a one year period combination therapy was associated with a nonsignificantly lower rate of progression than the comparator monotherapy group. The majority of the comparator group was on a statin, usually simvastatin, but the diversity of statin treatments in this group makes interpretation somewhat difficult.[175] While the accumulated evidence suggests that raising HDL-c levels may be helpful in high risk populations, the target levels and optimal strategies remain unknown.

Carotid intima-media thickness

Two trials investigated this outcome measure in participants in need of intensive lipid lowering therapy. One compared niacin-statin combination with background statin monotherapy (ARBITER-2) while the other investigated 80 mg of simvastatin plus 10 mg of ezetimibe, compared with 80 mg of simvastatin alone (ENHANCE trial). No significant differences were found between the treatments. No evidence was found pertaining to the question of lower dose statin in combination versus higher dose monotherapy for CIMT. The ENHANCE trial was similar in design to the 2-year ASAP trial that showed significant regression in CIMT with atorvastatin 80 mg compared with simvastatin 40 mg.[222]. Important differences can be recognized between the ASAP and ENHANCE trials, including a higher baseline CIMT and inclusion of statin naïve participants in ASAP. Further, as pointed out by Brown and Taylor none of the intervention studies on CIMT of 2 years or less duration have demonstrated an effect.[32]The questions surrounding the findings of the ENHANCE trial will require further long term studies focused on clinical outcomes.

Adherence and Harms

Scant evidence exists comparing short term harms and treatment adherence for lower dose statin in combination with higher dose monotherapy across all populations. Comparing statin combination therapies with monotherapy using similar statin doses, significantly fewer participants adhered to pravastatin plus cholestyramine combination treatment as determined by pill counts (OR, 0.41, 95% CI 0.26, 0.70), and proportionally more withdrew from statin plus

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BAS and statin plus niacin combinations (pooled ORs 2.77; 95% CI 1.16, 6.60 and 2.24; 95% CI 1.37, 3.68 respectively).

A common adverse event with niacin is flushing, reported by as many as 88% of individuals initiating slow release niacin.[223] Of note however, the absolute rates of withdrawal in niacin plus statin treatment groups in these trials were lower, in the range of 3-22%. There were also high rates of adverse events with statin plus BAS combination therapy.

No participant developed rhabdomyolysis across all 87 RCTs investigating 5 statin combination therapies. These result are recognized in and consistent with extant literature.[224] However, this lack of evidence fails to shed light upon the relative safety of lower dose statin in combinations, compared with higher dose monotherapy.

Medication adherence is a significant issue in determining population benefit. In a population based cohort study Sokol demonstrated an association between medication adherence, and lower medical costs and reduced hospitalization rates in individuals with hypercholesterolemia.[225] In general, medication nonadherence rates range from 20% to 50%.[226,227] Chronic conditions and preventive therapies are associated with poorer adherence rates than acute conditions.[227] The complexity of medication regimen and the number of medications may play a role in adherence.[228,229] Thus there may be benefit from less complex regimens employing fewer separate agents. Medication adherence and persistence are related but distinct concepts which have recently been clarified. Adherence is defined as the extent to which an individual acts in accordance with the prescribed interval and dose of a dose regimen while persistence is the accumulation of time from initiation to discontinuation of therapy.[230] The previous literature uses the terms interchangeably. While this report refers to adherence, this outcome was rarely reported and for most reports we could only extract data regarding the proportion of participants withdrawing from treatment.

Subgroups

There is dearth of available evidence regarding lower dose statin in combination therapy versus higher dose monotherapy in subgroups. Absence of evidence or at best scant trial evidence precluded definitive conclusions regarding short term and longer term efficacy.

With few exceptions, included trials were mixed with respect to gender, but no subgroup data in women were available for extraction. Most trials were comprised of a majority white population of European descent. Goff in a multicenter cohort study reported that the prevalence of dyslipidemia was similar in populations of African and Hispanic descent in the US, but that they were less likely to be treated or controlled.[231] Mexican Americans are significantly less likely than non-Hispanic whites to be aware of and treated for dyslipidemia despite having a prevalence only slightly lower. While socioeconomic and access issues impact treatment and control, members of both populations fall into groups who require lipid modifying treatment and trials of these therapies should reflect that reality.

The average age of participants was in the fifties, limiting generalizability to older populations. Deedwania compared moderate statin therapy (pravastatin 40 mg) and intensive therapy (atorvastatin 80 mg) in individuals aged 65-85 with coronary artery disease. The atorvastatin group had fewer deaths and major cardiac events, though there was an increase in the proportion with elevated hepatic enzymes.[232] Trials of combination therapy need to involve

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the larger population of Americans at older ages who require therapy, to confirm efficacy and tolerability.

Long-term non-randomized studies directly investigating clinical effectiveness, serious adverse events and cancer were also lacking. Sparse event data in the three included studies could not guide any definitive conclusions.

Limitations

Our review does not examine specifically the addition of a combination medication to maximal statin therapy. There are instances, such as familial dyslipidemia, in which combinations may be required to achieve target levels.

The assessments of clinical outcomes, harms and treatment adherence were limited by the paucity of long term studies with a sufficient number of events to offer meaningful results. The search for specific harms was limited to prespecified important events rather than all potential adverse experiences. Thus studies investigating specific minor adverse experiences were not captured unless adverse events lead to nonadherence or withdrawal from treatment. Composite outcomes were rarely reported in the included trials and imputation was not attempted as the possibility of double counting could not be avoided. We used a conservative approach to pooling with a strict limit to allowable heterogeneity which precluded pooling of results in a number of instances.

A number of caveats apply to the evaluation of surrogate outcomes. First, the absolute benefit in measures of LDL-c and HDL-c may depend on the baseline status, including intensity of statin therapy and comorbidities. In conducting our review we used percentage change from baseline as that was most commonly reported, as well as change scores and post treatment means if data permitted. Percentage change from baseline has lower statistical power and may fail to protect against bias in the case of baseline imbalances.[233]

Indirect comparisons are hazardous given the potential differences in trial populations and design. Indirect comparisons may inflate estimates of differences and were not attempted.[234]

A large number of studies were funded by pharmaceutical companies. Evidence suggests that industry sponsorship of research is associated with a greater likelihood of results favoring the sponsored product.[235,236] We did not detect many instances of possible publication bias based upon funnel plots in this review, but the power to detect was limited.

A number of concerns regarding trial quality were identified. Only 26 of 87 (30%) included randomized controlled trials reported allocation concealment and 21 (24%) reported an intention to treat analysis. Clinical end points were rarely adjudicated and blinding not consistently reported.

Conclusion

Combination therapy may become more common, to achieve the lower targets for LDL-c and to elevate HDL-c in high risk individuals. The trend toward more stringent targets and identification of coronary heart disease risk equivalents increases the number of Americans who may benefit from these therapies.

It is unlikely that a single therapeutic strategy will be optimal for all individuals, and future research will be targeted to specific clinical and lipid profiles. A number of questions remain as

to the optimal strategies combining efficacy, safety and adherence for lipid modification in those requiring intensive therapy. Long term trials with clinical outcomes are required to resolve these issues. At present however the evidence does not support routine use of any studied combination over higher dose statin therapy.

Ezetimibe GRADE tables

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Table 40. GRADE: lower dose simvastatin combination therapy versus higher dose simvastatin monotherapy in participants requiring intensive lipid-lowering therapy

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (followup 24 weeks)				
1	0/104 (0%)	0/110 (0%)	-	-
Vascular death - not measured				
0	-	-	-	-
Participants reaching ATP III LDL-c goals (followup 23-24 weeks)				
2[3]	118/146 (80.8%)	160/281 (57%)	OR 3.55 (2.18 to 5.79)	low[1,2]

[1] 2 trials, one with adequate allocation concealment and double-blind procedure,[38] no intention-to-treat analysis was described.[38,116]
[2] All participants required intensive lipid-lowering therapy because of type 2 diabetes mellitus
[3] Both studies compared simvastatin (20 mg/day) plus ezetimibe (10 mg/day) with simvastatin monotherapy (40 mg/day)

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

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Table 41. GRADE: statin plus ezetimibe therapy versus statin monotherapy in participants requiring intensive lipid-lowering therapy

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (followup 6-24 weeks)				
9[1]	2/1470 (0.1%)	4/1486 (0.4%)	OR 0.6 (0.15 to 2.39)	very low[1,2,3]
Vascular death (followup 96 weeks)				
1	2/357 (0.6%)	1/363 (0.3%)	OR 2.04 (0.18 to 22.6)	very low[4]
Participants reaching ATP III LDL-c goals (followup 6-24 weeks)				
14	2826/3492 (80.9%)	1372/2708 (50%)	not pooled	very low[5,6]

[1] Four trials reported no deaths.[109,111,116,123]
[2] One long-term [116] and 8 short-term trials,[109-111,123,125-127,173] two with adequate allocation concealment,(6171, 13142} three with adequate double-blind procedure,[109-111] and one reported intention-to-treat analyses[123]
[3] Wide confidence intervals in each single trial and pooled data
[4] Single study with 96 weeks followup, adequate allocation concealment and reporting three vascular deaths.(16384} Double-blind, and intention-to-treat analysis procedures were not reported.[33]
[5] All short-term trials,[38,102,104,109-112,116,123,125,127,148,150,173] four with adequate allocation concealment,(317, 6171, 13142, 16386} four with adequate double-blind procedure,[104,109-111] and three reported intention-to-treat analyses[104,123,150]
[6] Results not pooled because of significant heterogeneity (I-squared 94%)

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

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Table 42. GRADE: statin plus ezetimibe therapy versus statin monotherapy in participants with baseline LDL-c > 190 mg/dL

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality - not measured				
0	-	-	-	-
Vascular death (followup mean 96 weeks)				
1	2/357 (0.6%)	1/363 (0.3%)	OR 2.04 (0.18 to 22.6)	very low[1]
Participants reaching ATP III LDL-c goals - not measured				
0	-	-	-	-

[1] Single study with 96 weeks followup, adequate allocation concealment and reporting three vascular deaths.(16384} Double-blind, and intention-to-treat analysis procedures were not reported.[33]
Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

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Table 43. GRADE: statin plus ezetimibe therapy versus statin monotherapy in participants with diabetes mellitus

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (followup 6-24 weeks)				
3[1]	1/936 (0.1%)	2/951 (0.2%)	OR 0.49 (0.06 to 4.02)	very low[1,2]
Vascular death - not measured				
0	-	-	-	-
Participants reaching ATP III LDL-c goals (followup 6-24 weeks)				
6	1646/2019 (81.5%)	724/1433 (50%)	not pooled	very low[3,4]

[1] A single trial with followup of 24 weeks reported no deaths.[116] Data from two trials reporting 3 deaths were pooled.[127,173]
[2] Two short-term trials with adequate allocation concealment,[127,173] none with adequare double-blind procedure or intention-to-treat analysis
[3] All short-term trials,[110,112,116,127,148,173] three with adequate allocation concealment,[112,127,173] one with adequate double-blind procedure,[110] and none with intention-to-treat analysis
[4] Short-term trials with significant heterogeneity (I-squared = 92%)
Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

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Table 44. GRADE: statin plus ezetimibe therapy versus statin monotherapy in participants with established vascular disease

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (followup mean 6)				
5[1]	0/757 (0%)	2/782 (0.2%)	OR 0.34 (0.04 to 3.25)	very low[1,2]
Vascular death - not measured				
0	-	-	-	-
Participants reaching ATP III LDL-c goals (followup 6-12 weeks)				
5	616/759 (81.2%)	211/779 (27%)	not pooled	very low[3,4]

[1] All short-term trials, with unclear allocation concealment,[109-111,123,126] three with adequate double-blind procedure,[109-111] and one reported intention-to-treat analysis.[123]
[2] Three trials reported no deaths.[109,111,123]
[3] All short-term trials, with unclear allocation concealment,[109-111,123,150] three with adequate double-blind procedure,[109-111] and two reported intention-to-treat analysis.[123,150]
[4] All studies favored combination therapy, however, due to significant heterogeneity (I-squared 72%) data was not pooled.

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

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Table 45. GRADE: statin plus ezetimibe therapy versus statin monotherapy in participants of African descent

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (followup mean 12 weeks)				
1	0/124 (0%)	0/123 (0%)	-	very low[1,2]
Vascular death - not measured				
0	-	-	-	-
Participants reaching ATP III LDL-c goals (followup mean 6 weeks)				
1	85/135 (63%)	24/73 (33%)	OR 3.47 (1.9 to 6.33)	very low[1,2]

[1] A single RCT with no deaths in combination or monotherapy was identified[128]
[2] adequate allocation concealment and double-blind procedure, no intention-to-treat analysis[128]

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

Table 46. GRADE: statins plus ezetimibe versus statins monotherapy in participants of Hispanic descent

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality - not measured				
0	-	-	-	-
Vascular death - not measured				
0	-	-	-	-
Participants reaching ATP III LDL-c goals (followup mean 6 weeks)				
1	46/71 (64.8%)	8/42 (19%)	OR 7.82 (3.14 to 19.45)	very low[1]

[1] Data from a sub-group population of a single trial.[112] Main RCT with adequate allocation concealment and double blind, no intention-to-treat analysis performed.

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

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Table 47. GRADE: lower dose simvastatin plus ezetimibe therapy versus higher dose simvastatin monotherapy in all participants

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (followup 24 weeks)				
1	0/104 (0%)	0/110 (0%)	-	-
Vascular death (followup 12 weeks)				
1	1/58 (1.7%)	0/63 (0%)	OR 3.31 (0.13 to 82.96)	very low[1,2]
Serious adverse events (followup 23-24 weeks)				
2	28/464 (6%)	13/363 (3.6%)	OR 1.86 (0.6 to 5.74)	very low[3,5,6]
Participants reaching ATP III LDL-c goals (followup 23-24 weeks)				
2	118/146 (80.8%)	160/281 (49%)	OR 3.55 (2.18 to 5.79)	low[3,4]

[1] 1 trial reporting one death during a 12 weeks followup.[135] This trial had an adequate allocation concealment and double-blind procedure, no intention-to-treat analysis was described
[2] 2 of the 8 arms presented contributed data for this outcome[135]
[3] 2 trials one with adequate allocation concealment and double-blind procedure,[38] no intention-to-treat analysis was described.[38,116]
[4] All participants required intensive lipid-lowering therapy because of type 2 diabetes mellitus
[5] All participants required intensive lipid-lowering therapy because of type 2 diabetes mellitus[116] or CHD risk equivalent[38]
[6] Wide confidence intervals in each single trial and pooled data

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

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Table 48. GRADE - statin plus ezetimibe therapy versus statin monotherapy in all participants followed for more than 24 weeks

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (followup 24-52 weeks)				
4	3/98 (3.1%)	0/102 (0%)	OR 7.51 (0.38 to 147.37)[3]	very low[1,2,3,4]
Vascular death (followup 96 weeks)				
1	2/357 (0.6%)	1/363 (0.3%)	OR 2.04 (0.18 to 22.59)	very low[6,7]
Serious adverse events (followup 24-52 weeks)				
7	137/1329 (10.3%)	54/564 (10%)	not pooled	very low[8,9,10]
Participants reaching ATP III LDL-c goals - not measured				
0	-	-	-	-

[1] Results based on 3 deaths, and only one trial with analysable data[147]
[2] 3 trials reported no deaths[39,116,130]
[3] 2 trials described adequate allocation concealment,[116,147] none described adequate double-blind, and 1 trial described intention-to-treat analysis[147]
[4] Participants with renal disease and without definitive indication for cholesterol lowering
[5] all participants presented with baseline LDL-c >190 mg/dL
[6] study with adequate allocation concealment, double-blind, no intention-to-treat analysis described[33]
[7] 1 trial reported 3 vascular deaths in a 96 weeks followup[33]
[8] 3 trials described adequate allocation concealment,[39,135,147] none described adequate double-blind, and 1 trial described intention-to-treat analysis[147]
[9] Results not pooled because of significant heterogenity (I-squared = 77%)
[10] SAE were reported by only half of the trials and from these 6 had a long-term followup

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

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Table 49. GRADE - statin plus ezetimibe therapy versus statin monotherapy in all participants

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (followup 6-52 weeks)				
17	5/1568 (0.3%)	4/1588 (0.2%)	OR 0.94 (0.27 to 3.3)	very low[1,2,3]
Vascular death (followup 12-96 weeks)				
2	3/415 (0.7%)	1/416 (0.2%)	OR 2.28 (0.33 to 15.68)	very low[4,5]
Serious adverse events (followup 6-52)				
20	229/5907 (3.9%)	132/5221 (2.5%)	OR 1.07 (0.82 to 1.39)	low[9,10]
Participants reaching ATP III LDL-c goals (followup 6-24 weeks)				
21	6669/8271 (80.6%)	4187/6922 (60%)	not pooled	very low[6,7,8]

[1] 11 trials reported no deaths,[39,109,111,112,116,123,128,130,132,134,172] 3 trials described adequate allocation concealment,[127,147,173] 1 trial described adequate double-blind,[110] , and 1 trial described intention-to-treat analysis[147]
[2] Results based on 9 deaths, and only one trial with analysable data had a followup of > 24 weeks[147]
[3] Only 17 of the 37 included trials provided data on all cause mortality
[4] Only 2 out of 37 included trials reported 4 events of vascular death.[33,135] Both studies described adequate allocation concealment, did not describe the procedure for double-blind or intention-to-treat analysis.
[5] Results based on 4 deaths, and only one trial with analysable data had a followup of > 24 weeks[33]
[6] 8 trials described adequate allocation concealment,[104,112,113,127,132,135,172,173] 2 trials described adequate double-blind,[104,111] , and 6 trials described intention-to-treat analysis[104,123,132,134,140,150]
[7] Results based only on short-term trials, with significant heterogenity (I-squared = 94%)
[8] 21 out of 37 studies reported this outcome
[9] 7 trials described adequate allocation concealment,[39,127,128,135,147,149,172] 4 trials described adequate double-blind,[109,111,128,149] , and 4 trials described intention-to-treat analysis[123,140,147,150]
[10] 20 out of 37 included trials reported this outcome

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

Fibrate GRADE tables

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Table 50. GRADE: Rosuvastatin (5-10 mg/day) plus fenofibrate (67 mg/day) versus rosuvastatin (40 mg/day) in participants requiring intensive lipid-lowering therapy because of diabetes mellitus

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (follow-up 18 weeks)				
1	1/113 (0.9%)	1/53 (1.9%)	OR 0.46 (0.03 to 7.57)	very low[1,2]
Vascular death - not measured				
0	-	-	-	-
Serious Adverse Events - not measured				
0	-	-	-	-
Participants reaching ATPIII LDL-c goals (follow-up 18 weeks)				
1	83/110 (75.5%)	43/50 (86%)	OR 0.5 (0.2 to 1.24)	very low[1,2]

[1] Single study with unclear allocation concealment, no intention-to-treat analysis reported, short-term followup, and very sparse number of events
[2] Only one of the 11 included trials compared lower dose statin combination with higher dose monotherapy

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

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Table 51. GRADE - statin plus fibrate therapy versus statin monotherapy in participants requiring intensive lipid-lowering therapy

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (follow-up 18 weeks)				
1	1/113 (0.9%)	1/53 (1.9%)	OR 0.46 (0.03 to 7.57)	very low[1,2,3]
Vascular death - not measured				
0	0/0	0/0	-	-
Serious Adverse Events (follow-up 52 weeks)				
1	0/25 (0%)	0/23 (0%)	-	very low[3]
Participants reaching ATPIII LDL-c goals (follow-up 18-24 weeks)				
2	122/150 (81.3%)	75/90 (83%)	not pooled	very low

[1] Single study with unclear allocation concealment, no intention-to-treat analysis reported, short-term followup, and very sparse number of events
[2] All participants had diabetes mellitus
[3] Only one of the 5 trials performed in high risk population reported this outcome

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

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Table 52. GRADE: statin plus fibrate therapy versus statin monotherapy in participants with diabetes mellitus

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (follow-up 18 weeks)				
1	1/113 (0.9%)	1/53 (1.9%)	OR 0.46 (0.03 to 7.57)	very low[1,2,3]
Vascular death - not measured				
0	-	-	-	-
Serious Adverse Events - not measured				
0	-	-	-	-
Participants reaching ATPIII LDL-c goals (follow-up 18-24 weeks)				
2	122/150 (81.3%)	75/90 (83%)	not pooled	very low[2,3,4,5]

[1] Single study with unclear allocation concealment, no intention-to-treat analysis reported, 18 weeks followup, and very sparse number of events
[2] Results based on two short-term trials, with significant heterogeneity (I-squared = 84%)
[3] Only one of the 5 trials performed in high risk population reported this outcome
[4] All trials with unclear allocation concealment, none double-blind, one reported intention-to-treat analyses[143]
[5] Results based on a sub-group of 2 out of 11 included trials

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

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Table 53. GRADE - statin plus fibrate therapy versus statin monotherapy in all participants

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (follow-up 12-18 weeks)				
3	1/188 (0.5%)	2/124 (1.4%)	OR 0.39 (0.05 to 3.22)	very low[1,2,3,4]
Vascular death - not measured				
0[5]	-	-	-	-
Serious Adverse Events (follow-up 12-52 weeks)				
2	12/428 (2.8 %)	5/224 (1.2%)	OR 1.2 (0.42 to 3.46)	very low[9,10]
Participants reaching ATPIII LDL-c goals (follow-up 18-24 weeks)				
2	122/150 (81.3%)	75/90 (83%)	not pooled	very low[5,6,7,8]

[1] All trials with unclear allocation concealment, one double-blind,[105] none reported intention-to-treat analyses
[2] Results based on sparse number of events, three trials with short-term follow up
[3] Small sample size (individual trials and pooled data), wide confidence intervals
[4] Only 3 out of 11 included trials provided data on all cause mortality
[5] All trials with unclear allocation concealment, none double-blind, one reported intention-to-treat analyses[143]
[6] Results based on two short-term trials, with significant heterogenity (I-squared = 84%)
[7] All participants had diabetes mellitus and might have increased risk
[8] Results provided in only two out of 11 included trials
[9] One trial of unclear allocation concealment,[118] one trial did not reported intention-to-treat analysis[115]
[10] Results based on two small trials and sparse number of events

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

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Niacin GRADE tables

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Table 54. GRADE: Statin plus niacin therapy versus statin monotherapy, in participants requiring intensive lipid-lowering therapy

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (follow-up 52 weeks)				
1	2/78 (2.6%)	1/71 (1.4%)	OR 1.84 (0.16 to 20.76)	very low[1,2,3]
Vascular death (follow-up 12 weeks)				
1	0/27 (0%)	0/27 (0%)	-	-
Serious Adverse Events - not measured				
0	-	-	-	-
Participants reaching ATPIII LDL-c goals (follow-up 16 weeks)				
1	21/32 (65.6%)	19/34 (56%)	OR 1.51 (0.56 to 4.08)	very low[2,4]

[1] Single study with adequate allocation concealment and double-blind procedure, no intention-to-treat analysis reported, long-term followup, and 3 deaths[175]
[2] All participants had established vascular diseases
[3] Only one of the 6 trials performed in high risk population reported this outcome
[4] 1 short-term trial with unclear allocation concealment, double-blind procedure, and no description of intention-to-treat analysis.[40]

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

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Table 55. GRADE: Statin plus niacin therapy versus statin monotherapy, in all participants

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (follow-up 17-52 weeks[1])				
4	3/192 (1.6%)	2/132 (1.5%)	OR 1.08 (0.17 to 6.72)	low[2,3,4]
Vascular death (follow-up 12-28 weeks[5])				
2	1/114 (0.9%)	1/61 (1.6%)	OR 0.53 (0.03 to 8.64)	very low[6,7]
Serious Adverse Events (follow-up 17-28 weeks)				
3	11/274 (4%)	3/154 (3%)	OR 1.63 (0.48 to 5.56)	very low[10,11]
Participants reaching ATPIII LDL-c goals (follow-up 16 weeks)				
1	78/105 (74.3%)	78/117 (83%)	Not pooled[9]	very low[8,9]

[1] Only the two long-term studies contributed data to the pooled analysis.[96,175]
[2] 2 long-term trials with adequate allocation concealment, adequate double-blind procedure, and intention-to-treat analysis was described.[96,175]
[3] Results based on two studies and 5 deaths.
[4] Two short-term trials reported no deaths.[95,151]
[5] Only the long-term trial contributed data to the analysis.[133]
[6] 2 trials with unclear allocation concealment,[133], 13487} one long-term trial with adequate double-blind procedure and intention-to-treat analysis described[133]
[7] One short term trial reported no death.[176]
[8] 1 short-term trial with unclear allocation concealment, double-blind procedure, and no description of intention-to-treat analysis.[40]
[9] Data is provided in four arms of the same trial, but with significant heterogeneity (I-squared = 63%)
[10] 1 long-term[96] and 2 short-term[95,151] trials, 2 with adequate allocation concealment, adequate double-blind procedure, and description of intention-to-treat analysis,[95,96]
[11] Wide confidence intervals in each single trial and pooled data
Abbreviations: OR = odds ratio, CI = 95% confidence interval

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

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Bile Acid Sequestrants GRADE tables

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Table 56. GRADE - statin plus BAS therapy versus statin monotherapy in all participants

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (follow-up 4-24 weeks)				
3	1/73 (1.4%)	1/78 (1.3%)	OR 1.07 (0.11 to 10.51)	very low[1,2,3]
Vascular death - not measured				
0	0/0	0/0	-	-
Serious Adverse Events (follow-up 6-30 weeks)				
2	1/112 (0.9%)	6/166 (3.3%)	OR 0.39 (0.06 to 2.36)	very low[1,7,8]
Participants reaching ATPIII LDL-c goals (follow-up 12 weeks, all participants required lipid lowering therapy because of established vascular diseases)				
1	13/28 (46.4%)	5/31 (16%)	OR 4.51 (1.34 to 15.1)	very low[5,6]

[1] One trial had an adequate allocation concealment and adequate double-blind,[152] and no trial used an intention-to-treat analysis
[2] Results based on sparse number of events, two trials with short-term follow up
[3] Only 3 out of 17 included trials provided data on all cause mortality
[4] Analysis based on a single trial on which all participants required intensive lipid-lowering therapy because of established vascular diseases[99]
[5] One trial, unclear allocation concealment, no double-blind, no intention-to-treat analysis; short-term followup, and small sample size.[99] All participants required lipid lowering therapy because of established vascular diseases.
[6] Results provided in only one out of 17 included trials
[7] Results based on sparse number of events, two trials one with short-term follow up[152]
[8] In one trial all participants had LDL-c >190 mg/dL at baseline[177]

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

Omega-3 fatty acids GRADE tables

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Table 57. GRADE: Statin plus Omega-3 therapy compared with statin monotherapy, in participants of Asian origin

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (follow-up 240 weeks)				
1	286/9469 (3%)	265/9471 (2.8%)	OR 1.08 (0.91 to 1.28)	moderate[2,3]
Vascular death - not measured				
0	-	-	-	-
Serious Adverse Events - not measured				
0	-	-	-	-
Participants reaching ATPIII LDL-c goals - not measured				
0	-	-	-	-

[1] One long-term trial with adequate allocation concealment and intention-to-treat analysis was described, no double-blind procedure reported.[124]

Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

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Table 58. GRADE: Statin plus Omega-3 therapy compared with statin monotherapy, in all participants

Number of studies	Participants with events – combination therapy	Participants with events – statin monotherapy	Relative Effect (95% CI)	Quality
All cause mortality (follow-up mean 240 weeks[1])				
3	286/9469 (3%)	265/9471 (2.8%)	OR 1.08 (0.91 to 1.28)	moderate[2,3]
Vascular death - not measured				
0	-	-	-	-
Serious Adverse Events (follow-up mean 8 weeks)				
1	4/122 (3.3%)	1/132 (0.8%)	OR 4.44 (0.49 to 40.29)	very low[4]
Participants reaching ATPIII LDL-c goals - not measured				
0	-	-	-	-

[1] Three studies included, but only one long-term trial wit large sample size contributed data to the pooled analysis.[124]
[2] One long-term trial with adequate allocation concealment and intention-to-treat analysis was described, no double-blind procedure reported.[124]
[3] Two short-term trials reported no deaths.[157,160]
[4] One short-term trial with adequate allocation concealment and double-blind procedure, no intention-to-treat analysis was reported.[160]
Abbreviations: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals, CI = 95% confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation OR = odds ratio

Table 59. Overall summary of comparative syntheses of statins plus non-statin drug combination therapy compared with statin monotherapy

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 co-administration 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 impact was noted for omega-3 fatty acids, ezetimibe and fibrates on mortality. No evidence for the other agents.
Vascular death	very low	No evidence was available for any combination.
Serious adverse events	very low	Combination therapies do not demonstrate an increase in adverse events over statin monotherapy. Ezetimibe studies are of sort duration while all other agents have limited numbers of studies and participants.
Key Question 2: Do these regimens differ in reaching LDL-targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?		

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Attainment of ATP III LDL-c goals	low	Ezetimibe plus simvastatin therapy is more likely to result in attainment of LDL-c target than higher dose simvastatin, based on two small trials.
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	very low	No benefit or harm is noted for any combination in any subgroup. There is insufficient data on ethnic origin for all therapies apart from one large trial demonstrating no impact of omega 3 combination therapy on mortality in an Asian population. There is no data for BAS and niacin for this outcome in any prespecified subgroup.
Vascular death	very low	No benefit or harm for ezetimibe combinations for high risk participants or those with LDL-c above 190 mg/dL, based on one long term trial.
Serious adverse events[7]	low	No increased risk identified based on a limited number of trials most of short duration.
Attainment of ATP III, LDL-c goals[8]	low	Ezetimibe plus statin combination therapy demonstrated a greater probability of goal attainment than any dose statin monotherapy for high risk participants with diabetes and/or established vascular disease. One small trial suggests benefit for those of Hispanic or African descent. Two trials of fibrate combinations are neutral for participants with diabetes mellitus and for all high risk participants. No other evidence is available.
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.

* GRADE was moderate for omega-3 fatty acids. No significant difference was seen, in all participants.
Abbreviations: ATP III = Adult Treatment Panel III (of the NCEP), GRADE = Grading of Recommendations Assessment, Development and Evaluation , LDL-c = low density lipoprotein cholesterol

Future Research

This review has identified a number of areas requiring future research. Our recommendations address research methodologies in general, and specific needs for research to address key questions

Research methodologies and reporting

All trials must ensure adequate allocation concealment and intention to treat analysis. Blinding and end point adjudication should be employed to minimize bias. Trial reports should follow the CONSORT statement.

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 co-administration of different lipid-modifying agents (i.e. a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

7. The comparator for trials of combination therapy in which LDL-c reduction or clinical events are a major outcome should be a higher dose statin in most instances. The bulk of

the clinical evidence for this endpoint as well as clinical endpoints exists for statin monotherapy. Until a compelling case can be made for a particular combination therapy, comparisons with lower doses of statins are unhelpful.

8. Studies of combination therapy should be conducted over longer time periods and be powered for clinical endpoints. The current evidence base lacks trials of this type, significantly limiting the conclusions which can be drawn.

9. Adverse events should be prospectively collected and comprehensively reported. Short duration trials are unlikely to accrue sufficient adverse events, particularly those with longer latency periods.

10. As the possibility of harm cannot be excluded for some individuals with symptomatic cerebrovascular disease, this population should be specifically studied in order to better define the parameters for those in whom intensive combination therapy is recommended.

11. Concomitant and antecedent therapy should be explicitly stated as both of these factors may influence outcomes. In studies employing a mixture of statin medications and/or doses, results should be reported by medication and dose in order to allow pooling across studies.

12. Studies targeting HDL-c elevation in a population with LDL-c at target are recommended. The absence of such evidence limits the ability to assess the role of combination therapies which raise HDL-c levels.

Key Question 2: Do these regimens differ in reaching LDL-targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

6. Reporting of surrogate measures should be consistent across all trials. In particular we recommend that the following be included in all reports: attainment of ATP 3 targets, and LDL-c, HDL-c, triglycerides as change scores or post treatment means.

7. The comparator for trials of combination therapy in which LDL-c reduction is major outcome should be a higher dose statin in most instances.

8. Studies to correlate LDL-c with CIMT and clinical outcomes should be conducted in different populations (e.g. participants with diabetes mellitus, CHD, and multiple risk factors as defined by ATP III), with reporting of antecedent therapy as this may be a determinant of outcome.

9. As medication adherence and persistence are important determinants of outcome and are correlated with the complexity of the treatment regimen, studies should be undertaken to compare combinations delivered as a single pill as opposed to two separate ones..

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10. Measures of adherence and persistence are affected by the duration of the study period and thus longer term trials are required for combination therapies of lipid modifying agents. A trial duration of greater than 6 months and preferably 1 year is recommended.

Key Question 3: Compared with higher dose statins, and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

3. Trials should be conducted in specific subgroups in order to determine relative benefits and harms. These groups include older individuals, participants with diabetes mellitus and multiple risk factors, and those of African, Hispanic and Asian descent.

4. Trials including women and the groups identified above should report results in a manner amenable to extraction and pooling in order to permit the early identification of a differential effect in specific subgroups.

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References

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Abbreviations

AAC	adequate allocation concealment
ACS	acute coronary syndrome
ALT	alanine transaminase
Apo	apolipoprotein
ApoA-I	apolipoprotein A-I
ApoA-II	apolipoprotein A-II
AST	aspartate transaminase
ATP III	Adult Treatment Panel III (of the NCEP)
Ator	atovastatin
AUC	area under the curve
bid	twice daily
c	calculated
CABG	coronary artery bypass graft
C-amine	cholestyramine
CCT	clinical controlled trial
CEA	carotid endarterectomy
C-lam	colesevelam
CHD	coronary heart disease
CIMT	carotid intima-medial thickness
Cmax	maximum plasma concentration
CPK	creatine phosphokinase
C-pol	colestipol
CT	conditional titration
CVD	cardiovascular disease
DHA	docosahexaenoic acid
dir	direct
DM	diabetes mellitus
eNOS	endothelial nitric oxide
EPA	eicosapentaenoic acid
ER	extended release (for niacin
Ez	ezetimibe
FF	fenofibrate
FH	familial hypercholesterolemia
FT	fixed titration
Fluv	fluvastatin
GF	gemfibrozil
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
h	hour
HC	hypercholesterolemia
HDL-c	high density lipoprotein cholesterol
HDL_2	subfraction 2 of HDL-c
HDL_3	subfraction 3 of HDL-c
HF	heart failure
hsCRP	high sensitivity C-reactive protein
HeFH	heterozygous familial hypercholesterolemia
HMG CoA	hydroxymethylglutaryl coenzyme A
HoFH	homozygous familial hypercholesterolemia
HoFS	homozygous familial sitosterolemia
hsCRP	high sensitivity C-reactive protein
ITTA	intention to treat analysis
LDL-c	low density lipoprotein cholesterol
Lov	lovastatin
Lp(a)	lipoprotein A
max	maximum
MD	mean difference
MetS	metabolic syndrome
mFF	micronized fenofibrate
MI	myocardial infarction
nFH	non-familial hypercholesterolemia
NIH	National Institutes of Health
non-HDL-c	non-HDL cholesterol
NR	not reported
Om3	omega-3-acid ethyl esters
OL	open label
PCI	percutaneous coronary intervention
Pl	placebo
Prav	pravastatin
NCEP	National Cholesterol Education Program
NSAID	non-steroidal anti-inflammatory drug
od	once daily
OR	odds ratio
q	every

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RLP	remnant-like particle	T2DM	type 2 diabetes mellitus
Ros	rosuvastatin	TG	triglycerides
SB	single blind	TIA	transient ischemic attack
Sim	simvastatin	tid	three times daily
t½	half-life (time for concentration to decrease to half the initial level);	VLDL	very low density lipoprotein
		vs	versus
		wk	week(s)
T1DM	type 1 diabetes mellitus	y	year(s)

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