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Non-Statin Lipid Lowering Agents: Abbreviated Class Review

Month/Year of Review: April 2012
Classes Included: Bile Acid Sequestrants, Nicotinic Acid, Fibrates, Ezetimibe and Omega-3 fatty acid.

Reason for Review:
There are several classes of lipid lowing medications available with various mechanisms of action and pharmacokinetic properties. Although the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, known as statins remained to be the most widely prescribed lipid lowering medications, it could be difficult to obtain the low- density lipoprotein (LDL) treatment goal with a single statin for subset of patients with high baseline LDL or those who have developed adverse events from statin therapy. Recent new safety alerts including new restrictions, contraindications and dose limitations for high potency statins, such as simvastatin and rosuvastatin, were released by the FDA to reduce the risk of muscle injury. This may pose additional challenges in the management of lipid lowering. The other classes of lipid lowering agents have not been reviewed for the Preferred Drug List (PDL). This update will examine their place in therapy for these agents, and identify relevant comparative effectiveness evidence, high-quality systematic reviews, or evidence-based guidelines for consideration.

Conclusions:
Among other lipid lowering classes, agents from bile Acid Sequestrants (BAS), nicotinic acid, and fibrates have showed reduced major coronary events and/or total mortality or cardiovascular disease related deaths based on clinical trial results. Drugs from these classes can be treatment options for patients who cannot tolerate a statin or require additional lipid lowering in addition to a statin therapy to reach treatment goal. Evidence is lacking directly comparing drugs within each class.

Bile Acid Sequestrants (BAS): There is limited evidence comparing one agent to another. Cholestyramine has been shown to reduce major coronary events and coronary heart disease deaths, while all BAS (cholestyramine, colestipol, and colesevelam) have been shown to be effective in reducing LDL-C. Colesevelam has been studied in pediatrics ages 10 to 17 years of age. There is low quality evidence demonstrating no difference in mortality, vascular death, or severe adverse events when comparing the combination of a BAS and statin to statin monotherapy.

Fibrates: Gemfibrozil has demonstrated reductions in CV events and CHD mortality. As a class, the evidence is insufficient to show a reduction in all-cause mortality. Data from the ACCORD trial resulted in the FDA informing the public that fenofibric acid (Trilipix) may not lower a patient's risk of having a heart

attack or stroke in patients with diabetes. Fibrates are recommended in the management of patients with dyslipidemia and especially elevated triglycerides, which is consistent with ATP III recommendations. There is very low quality evidence that there is no difference in all cause mortality between the combination of a statin plus fenofibrate and statin monotherapy.

Nicotinic Acid: There is low quality evidence that no significant difference exists in all cause mortality, vascular death, or severe adverse events between the combination of niacin plus a statin versus statin monotherapy. Nicotonic Acid has been shown to reduce major coronary events and possibly mortality. Niaspan is an extended release form of niacin formulated to reduce the side effects.

Ezetimibe: To date, ezetimibe only has intermediate data on LDL lowering and no clinical data to support its value in reduced cardiovascular (CV) and stroke related outcomes.

Omega-3-fatty acids: Omega-3-fatty acid reduces triglycerides in patients with very high triglycerides (>500mg/dl) and although it appears to have a role in cardiovascular risk reduction, evidence remains inconclusive. In general, omega-3 fatty acid is an alternative to fibric acid derivatives and niacin for the treatment of high triglycerides. There is low quality evidence demonstrating no difference in all cause mortality or serious adverse events between the combination of a statin plus omega-3 and statin monotherapy.

Recommendations:

- Add Other Non-statin Lipotropics as a class to the PDL.
- Make cholestyramine a preferred bile acid sequestrant, which has shown improved CV related or stroke outcomes.
- Include gemfibrozil as a preferred lipotropic which has demonstrated improved CV related or stroke outcomes.
- Due to no evidence of clinical superiority of other fibric agents, prefer additional fibric acid products after price comparisons.
- Make Niaspan and Niacor preferred lipotropics due to a demonstrated reduction in cardiovascular outcomes.
- Make ezetimibe a non preferred lipotropic agent due to insufficient outcome data, and implement the non-preferred PDL prior authorization criteria for use.
- Make Lovaza a non preferred lipotropic agent and use the default non-preferred PDL prior authorization criteria due to its use as an alternative to a fibric acid derivative and niacin for hypertriglyceridemia.

Background:

Lipids (fats), together with proteins and carbohydrates, are the main components of living cells. Cholesterol and triglycerides are lipids that are stored in the body and served as a source of energy in addition to their role in cell structure. When cholesterol levels are high, fatty deposits can build up in the arteries, causing atherosclerosis. This can lead to heart disease and stroke. In the U. S, approximately one in every six adults has high cholesterol defined as total cholesterol of 240mg/dL or above.[1] It affects over 65 million Americans.[2] People with high cholesterol have double the risk for heart disease as people with lower levels. Evidence indicates levels of LDL correlate with the development of coronary heart disease (CHD), while the levels of high-density lipoprotein cholesterol (HDL) are associated with a lower risk of disease. The lowering LDL reduces CHD and stroke, which makes LDL a primary treatment target. In 2001,

the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) recommendations provide guidance on the targeted LDL goal based on patient's CHD risk.[3]

After the publication of ATP III guideline, 5 major clinical trials of statin therapy with clinical end points confirmed the benefit of cholesterol lowing therapy in high-risk patients with targeted LDL goal of less than 100mg/dL; moreover the findings from these trials suggested subset of patients with very high risk, additional benefit maybe obtained by reducing LDL levels to substantially below 100mg/dL.[4, 5] In light of this clinical trial evidence, in 2004, the National Cholesterol Education Program (NCEP) published ATP III updated recommendations to include an LDL goal of < 70mg/dL as a therapeutic option for patients at very high risk category.[6]

Issues:

- Is there reliable evidence showing lipid lowering agents besides statins reduce the risk of nonfatal myocardial infarcation (MI), CHD, mortality, stroke, or hospitalization?
- Is there evidence showing other classes of lipid lowering agents differ in benefits and harms within subgroups of patients?
- Is there any difference in effectiveness or harms among agents within the same lipid lowing class?

Methods:

A MEDLINE Ovid search was conducted using all lipid lower agents including: hyperlipidemia, hypercholesterolemia, cardiovascular disease, hydroxyl-3-methyglutaryl coenzyme A (HMG COA) reductase inhibitors, statin, ezetimibe, fibrates, nicotinic acid, niacin, bile acid sequestrant (BAS) and omega-3 fatty acids. The search was limited to randomized controlled trials and meta-analysis, English language, and to studies conducted in humans from September 2009 to present. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. Previous conclusions from guidelines and systematic reviews are listed in Appendix A, including an AHRQ systematic review from 2009 comparing the clinical outcomes of high-dose statin monotherapy with those of statin combination therapy in adults at high risk for coronary disease

Drugs Included in This Review

Drug		Dosage Form	Generic Availability
Bile Acid Sequestrants			
Cholestyramine (Questran®, Questran Light®)		9gm or 4gm (packet or scoop)	Yes
Colestipol (Cholestid®)		5gm/scoop granules or 1gm tablets	Yes
Colesevelam (Welchol®)		625mg tablets	No
Fibrates			
Gemfibrozol (Lopid®)		600mg tablets	Yes
Fenofibrate	Tricor®	48mg and 145mg tablets	Yes
	Lofibra®	54mg and 160mg tablts	Yes
	Lipofen®	50mg and 150mg capsules	No
	Triglide®	50mg and 160mg tablets	No
	Fenoglide®	40mg and 120mg tablets	No
Micronized fenofibrate	Lofibra® capsules	67mg, 134mg and 200mg capsules	Yes
	Antara®	43mg and 130mg capsules	Yes
Fenofibric Acid	Fibricor®	35mg and 105mg tablets	No
	Trilipix®	45mg and 135mg capsules	No
Nicotinic Acid			
Niacin IR (Niacor®)		500mg tablets	Yes
Niacin ER (Niaspan®)		500mg, 750mg and 1000mg tablets	No
Nicotinic acid (Slo-Niacin®) over-the-counter		50mg, 100mg, 250mg, 500mg, 750mg and 1000mg ER tablets	Yes
Omega-3 Fatty Acid			
Omega-3 fatty acid (fish oil) over-the-counter			Yes
Omega-fatty acid (Lovaza®)		1gm capsules	No
Ezetimibe			
Ezetimibe (Zetia®)		10mg tablets	No

New Systematic Reviews:
There were no new systematic reviews published within this review timeframe. In December 2010, the Cochrane Collaboration published a review protocol to assess the effectiveness of and safety of statins, exetimibe, fibrates, or fish oil for treating dyslipidemia in HIV-infected patients receiving highly active antiretroviral therapy. Clinical effectiveness was measured in terms of prevention (primary and secondary) of cardiovascular events (Fatal or nonfatal myocardial infarction, stroke and angina). [8]

New Guidelines:
In June 2011, the National Lipid Association Expert Panel on Familial Hypercholesterolemia published updated clinical guidance on screening, diagnosis and management of familial hypercholesterolemia (FH) in pediatric and adult patients. The guideline made the following drug treatment recommendations:

Drug Treatment Recommendations for adults:

- Both children and adults with LDL cholesterol ≥190 mg/dL [or non-high-density lipoprotein (HDL) cholesterol ≥220 mg/dL] after lifestyle changes will require drug therapy.
- For adult FH patients (≥20 years of age), drug treatment to achieve an LDL cholesterol reduction ≥50% should be initiated.
- Statins should be the initial treatment for all adults with FH.
- Higher risk patients may need intensification of drug treatment to achieve more aggressive treatment goals (LDL cholesterol < 100 mg/dL and non-HDL cholesterol < 130 mg/dL).
- Ezetimibe, niacin, and bile acid sequestrants are reasonable treatment options for intensification of therapy, or for those intolerant of statins.
- The potential benefit of multidrug regimens for an individual patient should be weighed against the increased cost and potential for adverse effects and decreased adherence.

Drug Treatment Recommendations in children:

- Statins are preferred for initial pharmacologic treatment in children after initiation of diet and physical activity management.
- Clinical trials with medium term follow up suggest safety and efficacy of statins in children.
- More aggressive LDL cholesterol targets should be considered for those with additional CHD risk factors.

Bile Acid Sequestrants (BAS):
BAS bind bile acids in the bowel. The bound bile acids are excreted in the feces, in turn it prevents re-absorption and depletion the intrahepatic pool of bile acids. BAS have been available for over 30 years. BAS are not absorbed in the intestine, hence do not have systemic side effects. However, these agents have significant gastrointestinal side effects such as constipation, frequent dosing and potential to interfere with absorption of other drugs and essential nutrition nutrients, which limit the use of these agents in practice. The BAS currently on the market include: cholestyramine (Qustran®, Qustran® light), colestipol (Colestid®) and colesevelam (Welchol®). Among all three agents, colesevelam is the latest BAS approved by FDA in May 2000. Both cholestyramine and colestipol

have shown clinical benefits in reducing CHD death, nonfatal myocardial infarction or stroke[9-11], whereas colesevelam has only demonstrated benefit on intermediate outcomes such as LDL reductions.

AHRQ Review BAS Conclusions (September 2009[7]):

- A total of four parallel group randomized trials compared statin plus BAS combinations and statin monotherapy that reported one or more clinical outcomes.
- Based on a single study in participants requiring intensive lipid lowering therapy, the grade of evidence is "very low" for an increase of participants reaching ATP III LDL-c goals for the combination of any dose statin plus BAS and high dose statin monotherapy (OR 4.51; 95% CI 1.34 to 15.14).
- Based on a single study in participants followed up for more than 24 weeks, the grade of evidence is "very low" for no difference in all cause mortality (OR 1.07; 95% CI 0.11 to 10.51) between the combination of any dose statin plus BAS and any dose statin monotherapy.
- Based on studies in participants regardless of baseline risk the grade of evidence is "very low" for no a difference in all cause mortality (3 trials; OR 1.07; 95% CI 0.11 to 10.51), no difference in serious adverse events (2 trials; OR 0.39; 95% CI 0.06 to 2.36) and an increase of participants reaching ATP III LDL-c goals (1 trial; OR 4.51; 95% CI 1.34 to 15.14).

New Systematic Reviews:
In March 2011, the National Lipid Association Expert Panel on Familial Hypercholesterolemia conducted a systematic review of BAS therapy in children with familial hypercholesterolemia[13]. In total, five clinical studies were identified that evaluated BAS monotherapy, whereas two studies were identified that evaluated combination therapy with a BAS and low-dose statin. The five BAS monotherapy studies showed a significant improvement in total cholesterol (percent change from baseline ranged from -7% to -14%) and LDL (percent change from baseline from -7% to -20%), but no significant change in HDL or TG. Only one studied evaluated colesevelam. Two combination therapy of BAS plus a statin studies (one study used cholestipol, one study used colesevelam as choice of BAS) showed significant improvement in total cholesterol (percent change from baseline ranged from -7% to -13%) and LDL (percent change from baseline from -5% to -17%). Change in HDL or TG are not significant. The main limitation of this review is that none of the studies were reviewed for quality or risk of bias. (Appendix B)

Conclusions:
The most recent AHRQ review indicated "very low" grade evidence for increasing the number of patients reaching LDL goals, no difference all cause mortality, and no difference in serious adverse events between BAS plus statin and statin monotherapy. However, when comparing BAS plus a statin with any dose statin with the older agents such as cholestyramine and colestipol, BAS plus a statin did demonstrate reduced major coronary events and CAD death. Colesevelam does not have cardiovascular clinical outcomes data. In addition, the recent treatment guideline from the National Lipid Association Expert Panel on Familial Hypercholesterolemia recommended BAS as treatment option for high-risk patients requiring intensive therapy or for those intolerant to statin therapy. ATP III guidelines also recommended combination of statin and BAS for patients with very high LDL.

Fibrates:

Unlike statins, fibrates do not work on lipid synthesis pathway. They reduce the levels of fatty acids by facilitating oxidation of these molecules. Two fibrates, gemfibrozil and fenofibrate or fibric acid derivative, are available in the U. S. Fibric acid derivatives inhibit triglyceride synthesis and stimulate catabolism of triglyceride-rich lipoproteins; whereas gemfibrozil inhibits peripheral lipolysis, decreases hepatic free fatty acid extraction, inhibits synthesis and increases clearance of VLDL carrier apolipoprotein B. Fibrates reduce triglyceride levels by 30-50% and may have beneficial effects on HDL and LDL levels depending on the baseline phenotype.[14] As statins do not have significant impact on triglyceride levels, use of these agents has been an option in populations with hypertriglyceridemia or mixed dyslipidemia, in place of or in addition to statins.[15] For individuals with diabetes or metabolic syndrome carry high CHD risk, fibrate therapy may be considered.[15]

Previous studies have demonstrated gemfibrozil to reduce the risk of CHD in patients with high TG and low HDL and more significantly in patients with diabetes. The combination of simvastatin and fenofibrate was not shown to reduce the rate of fatal CV events, nonfatal Mi, or nonfatal stroke, compared with simvastatin monotherapy in high-risk patients. In November 2011, the FDA informed the public that fenofibric acid (Trilipix) may not lower a patient's risk of having an MI or stroke, based on data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial.[16]

AHRQ Review Concluded (September 2009[7]):

- Based on a single study in participants requiring intensive lipid lowering therapy, the grade is "very low" grade for no difference in all cause mortality (OR 0.46, 95% CI 0.03 to 7.57), and the number of participants reaching ATP III LDL-c goals (OR not pooled) between the combination of lower dose statin plus fenofibrate and higher dose statin monotherapy.
- Based on studies in participants requiring intensive lipid lowering therapy, the evidence grade is "very low" quality evidence demonstrating no difference in all cause mortality (1 trial; OR 0.46, 95% CI 0.03 to 7.57), no difference in serious adverse events (1 trial, OR not reported) and no difference in the number of participants reaching ATP III LDL-c goals (2 trials, OR not pooled) between the combination of any dose statin plus fibrate and any dose statin monotherapy.
- Based on studies in participants with diabetes mellitus, the evidence grade is "very low" for no difference in all cause mortality (1 trial; OR 0.46, 95% CI 0.03 to 7.57) and the number of participants reaching ATP III LDL-c goals (2 trials; OR not pooled) between the combination of any dose statin plus fibrate and any dose statin monotherapy.
- Based on a one study in participants followed up for more than 24 weeks, the evidence grade is "very low" grade for difference in all cause mortality (1 trial; OR not reported), serious adverse events (1 trial, OR not reported) and the participants reaching ATP III LDL-c goals (1 trial, OR 9.75, 95% CI 1.16 to 82.11) between the combination of any dose statin plus fibrate and any dose statin monotherapy.
- Based on studies in participants regardless of baseline risk, the evidence grade is "very low" for no difference in all cause mortality (3 trials; OR 0.28, 95% CI 0.03 to 2.97), serious adverse events (2 trials; OR 1.2, 95% CI 0.42 to 3.46) and the number of participants attaining ATP III LDL-c goals (2 trials; OR not pooled) between the combination of any dose statin plus fibrate and any dose statin monotherapy.

New Systematic Reviews (Appendix B):

- Meng et al. published a meta-analysis in 2011 to examine the efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia.[17] Among the six trials that met selection criteria for inclusion, the authors found that compared to placebo, the greatest benefit with fibrate treatment was seen in 7,389 subjects with high triglycerides. Fibrate therapy reduced the risk of vascular events (RR 0.75, 95% CI 0.65 to 0.86, P < 0.001). In 5,068 subjects with both high triglycerides and low HDL-C fibrate therapy reduced the risk of vascular events (RR 0.71, 95% CI 0.62 to 0.82, P < 0.001). Less effect on vascular events was noted in 15,303 subjects selected for low HDL-C (RR 0.84, 95% CI 0.77 to 0.91, P < 0.001). Among 9,872 subjects with neither high triglycerides nor low HDL-C, fibrate therapy did not reduce subsequent vascular events (RR 0.96, 95% CI 0.85 to 1.09, P = 0.53). The fibrates that were used in the trials include gemfibrozil, fenofibrate and bezafibrate (not available in the U. S).

- Similar findings were also reported in another systematic review and meta-analysis by Bruckert E, et al in a Feb. 2011 publication.[18] The authors performed a computerized Pub Med literature search that focused on major randomized controlled trials evaluating fibrates in the prevention of cardiovascular disease, published between January 1966 and March 2010. In addition, authors also searched the reference lists of retrieved articles and of previously conducted systematic review and meta-analysis on lipid-lowering treatment for additional studies. The literature search identified 1239 citations. After reviewing the titles and abstracts, 21 articles were read in full and 8 eligible major randomized controlled trials were identified, and 5 trials were identified for analysis. The authors performed a meta-analysis of the 5 large trials assessing the impact of fibrates on cardiovascular end points and providing information on low HDL-C and high triglyceride levels. Subgroups were determined according to values closest to predetermined cut-offs for both HDL-C and triglycerides (<35 and >200 mg/dL, respectively). Overall, 4,671 patients (2,401 in fibrate group and 2,270 in placebo group) were classified as having an atherogenic dyslipidemia featuring low HDL-c combined with high triglyceride levels. Across trials, the proportion of patients classified in this subgroup ranged from 11% to 33%. A significant greater fibrate effect was found in high triglyceride levels subgroup (pooled RR, 0.72; 95% CI, 0.61to 0.85) in comparison with the counterpart subgroups (pooled RR, 0.94; 95% CI, 0.87 to 1.02, P for between-group heterogeneity = 0.002). A greater effect size was found in patients with high triglyceride levels or atherogenic dyslipidemia phenotype where fibrates were estimated to reduce the cardiovascular risk by 28% [95% confidence interval (CI), 15% to 39%; P < 0.001] or 30% (95% CI, 19% to 40%, P < 0.0001), respectively, but only by 6% (95% CI, 22% to 13%, P = 0.13) in nonatherogenic dyslipidemia patients. The authors concluded that targeting patients with high triglyceride levels or atherogenic dyslipidemia with fibrates may help reduce residual vascular risk. Fibrates that were evaluated included gemfibrozil (2 trials), fenofibrate (1 trial), fenofibrate + simvastatin (1 trial), and bezafibrate (1 trial).

Conclusions:

Although the AHRQ 2009 review indicated “very low” evidence level on various clinical outcomes comparing statin combination with fibrates vs. statin therapy, one significant limit of this review is that the trials included have heterogeneous characteristics of participants and most trials excluded participants with triglycerides above 300-600 mg/dL. The most recent systematic reviews focused on the clinical outcomes of patients with high triglycerides. Statins do not have significant role in reduction of triglycerides and gemfibrozil and fenofibrate have shown reduced vascular events in this situation. The most appropriate place in therapy for fibrates in the management of patients with dyslipidemia, are in those patients with especially elevated triglycerides, which is consistent with ATP III recommendation.

Nicotinic Acid

The exact mechanism of how niacin (nicotinic acid) reduces LDL and increases HDL is unknown. It is suspected to be involved in the metabolism of apolipoproteins, stimulating production of Apo A-I and Apo A-II, and possibly decreasing their turnover. It is also thought to decrease synthesis of LDL and VLDL without affecting fecal excretion of fats and bile acids.[19] Niacin was first introduced in 1954 and is available in immediate release, slow release and extended release forms. Flushing and rashes are common side effects associated with the use of niacin, which may occur in up to 60% of individuals.[20] However, this can be minimized by giving aspirin prior to niacin and slow titration of niacin dose.

The FDA announced in May 2011 a review of results from the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) clinical trial.[21] This trial compared simvastatin monotherapy to simvastatin + niacin extended release in patients with established CVD. The trial was halted early due to lack of incremental benefit on cardiovascular risk reduction in the niacin extended release group. Also, a small, unexplained, increase in the rate of ischemic stroke was noted in the combination group. At this time, FDA has made no new conclusions or recommendations regarding the use of extended-release niacin alone or in combination with simvastatin or other statins.[21]

Prospective observational cohort studies have confirmed the status of low high-density lipoprotein cholesterol (HDL-C) concentration as an independent risk factor for cardiovascular disease, which may partly account for the residual risk. The Inter Heart Study[22], a case–control study involving almost 30,000 participants in 52 countries, defined the proportion of the risk of adverse cardiovascular outcomes attributable to individual risk factors. In this analysis, an elevated ratio of apolipoprotein B to apolipoprotein A1, the principal apolipoproteins of LDL-C and HDL-C, respectively, accounted for more than half of the overall population-attributable risk for a first myocardial infarction. In addition HDL-C remains a strong predictor of the risk of having cardiovascular events in statin-treated patients who have reached their target LDL-C concentrations.[23] Niacin is the most potent lipid lowering agent that increases the HDL level. The analysis of the phase 3 trials of niacin-laropiprant 2 g shows reductions in triglycerides by 23%, 18% in LDL-C and a 20% increase in HDL-C.[24] Similar results were previously obtained with the Niaspan formulation of modified release niacin and with crystalline immediate-release niacin.[25] In the Coronary Drug Project (CDP), patients treated with nicotinic acid had significant reductions in coronary events compared with placebo-treated patients.[26, 27] A subsequent analysis on the relationship between on-treatment lipid values and outcomes in the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial study showed that for every 0.13 mmol/L (5 mg/dL) increase in HDL-C, there was an 11% relative risk reduction in coronary heart disease.[28] Niacin might be an attractive alternative for statin-intolerant patients and or in combination with statin.

AHRQ Review Concluded (September 2009[7]):

- Based on a single study in participants requiring intensive lipid lowering therapy, the evidence grade is “very low” demonstrating no difference in all cause mortality (OR 1.84; 95% CI 0.16 to 20.76) and no difference in participants reaching ATP III LDL-c goals (OR 1.51, 95% CI 0.56 to 4.08) between the combination of any dose statin plus niacin and to any dose statin monotherapy.
- Based on a single study in participants with established vascular disease, the evidence grade is “very low” demonstrating no significant difference in all cause mortality (OR 1.84, 95% CI 0.16 to 20.76), no difference in vascular death (OR not reported) and no difference in number of participants reaching ATP III LDLc goals (OR 1.51, 95% CI 0.56 to 4.08) between the combination of any dose statin plus niacin and any dose statin monotherapy.

- Based on studies in participants followed up for more than 24 weeks in mixed populations, the evidence grade is "very low" showing no significant difference in all cause mortality (4 trials; OR 1.08, 95% CI 0.17 to 6.72), no difference in vascular death (1 trial; OR 0.53, 95% CI 0.03 to 8.64) and no significant difference in serious adverse events (3 trials; OR 1.00, 95% CI 0.26 to 3.86) between the combination of any dose statin plus niacin and any dose statin monotherapy.
- Based on studies in participants regardless of baseline risk and comparing the combination of any dose statin plus niacin to any dose statin, "very low" grade for no difference in all cause mortality (6 trials; OR 1.08, 95% CI 0.17 to 6.72), no difference in vascular death (2 trials; OR 0.53, 95% CI 0.03 to 8.64), no difference in serious adverse events (5 trials; OR 1.29, 95% CI 0.44 to 3.80) and no difference in participants reaching ATP III LDL-c goals (1 trial, OR not pooled).
- The only significant difference was observed in change in HDL-C in participants requiring intensive lipid lowering therapy, favoring combination therapy (mean difference 13.00; 95% CI 6.01 to 20)

New Systematic Reviews (Appendix B):

- In 2010 Bruckert E et al. conducted a meta-analysis to examine the effect of niacin alone or in combination on CV events and atherosclerosis.[29] Among 587 citations, 29 full articles were read and 14 were eligible for inclusion. The authors identified ten randomized controlled trials that enrolled 2,647 patients in the active group and 3,898 patients in the control group. The largest trial accounted for 60% of the pooled sample.
  In the primary analysis, a significant response to treatment with niacin (alone or combined) was observed whatever the clinical outcome was. The relative odds reduction was 25% (95% CI = 14, 35) for major coronary events, 26% (95% CI = 8, 41) for stroke, and 27% (95% CI = 15, 37) for any cardiovascular event. A significant heterogeneity across studies was observed for any cardiovascular event. However, using a random-effect model, the effect size remained significant with a relative odds reduction of 48% (95% CI = 21, 65). Except for stroke, the pooled between-group difference remained significant in the sensitivity analysis excluding the largest trial. The authors concluded although the studies were conducted before statin therapy become standard care, and mostly in patients in secondary prevention, with various dosages of nicotinic acid 1–3 g/day, this meta-analysis found positive effects of niacin alone or in combination on all cardiovascular events and on atherosclerosis evolution. In addition to some inherent limitations of meta-analyses, the authors acknowledged that some of the clinical trials might have not been included in the review as the literature search was limited to Pub Med database only. However, for studies that were included in the analysis, the heterogeneity, sensitivity tests and the review of study quality and potential bias were conducted, although details on methods for quality assessment were not provided.
- Dugall JK et al. published a systematic review on March 5, 2010 on the effects of niacin on CV outcomes in patients with CAD, including randomized placebo-controlled trials.[30] There were 7 randomized control trials with total of 5,137 patients met the study inclusion criteria. Quality assessment was limited in this meta-analysis, including only concealment of the randomized treatment sequence and a follow-up of at least 90%.The analysis showed niacin therapy significantly reduced CAD revascularization compared to placebo (RR: 0.307 with 95% CI: 0.150 – 0.628; p = 0.001), nonfatal MI; (RR: 0.719; 95% CI: 0.603 – 0.856; p = 0.000), stroke and transient ischemic attack (TIA) (RR: 0.759; 95% CI: 0.613 – 0.940; p = 0.12), as well as possible but non-significant decrease in cardiac mortality (RR: 0.883; 95% CI 0.773 – 1.008; p = 0.066). The authors concluded that in this meta-analysis of 7 trials of secondary prevention, niacin was associated with a significant reduction in CV events and possible small but non-significant cardiovascular mortality.

Conclusions:
The main limitations of AHRQ review and the most recent reviews are 1) most trials included in the review were small and done prior to statin being used as first line; 2) the small numbers of end points in these older trials. Despite these limitations, niacin did show a positive effect on cardiovascular events. It remains to be the most potent agent to increase the HDL, which is a strong predictor of the risk of having cardiovascular events in statin-treated patients who have reached their target LDL-C concentrations. There is role of niacin especially in patients who cannot tolerate statin therapy. Niaspan® is extended released form of niacin formulated to reduce the side effects, especially flushing and rashes from the immediate release or slow release formulation of niacin.

Ezetimibe
Ezetimibe is an agent that inhibits intestinal absorption of cholesterol at the small intestine brush border by acting on the sterol transporter NPC1L1.[31] In clinical trials when used as monotherapy, it has shown to reduce LDL-c by 18% approximately.[32] It has minimal effects on TG and increases HDL modestly. Because it has different mechanism of action and works on absorption of cholesterol, the combination therapy using statin plus ezetimibe has the potential to influence both biosynthetic pathway and absorption, resulting a greater reduction in LDL-c levels with either agent alone. However, up to date, the greater degree of LDL-c level reduction when ezetimibe used in combination with statin has not demonstrated better clinical outcomes such as reduction in CV events, stroke or mortality. In addition, three recent clinical trials, ENHANCE[33], SEAS[34], and ARBITER 6-HALTS[35] have raised questions about the efficacy and safety of ezetimibe and have led to a re-examination of its clinical use as a drug for managing lipid risk factors. Both ENHANCE and ARBITER 6-HALTS trials showed no change in carotid intima-media thickness, a surrogate marker for arthrosclerosis. SEAS trial raised the potential of cancer risk from ezetimibe. See Appendix C for abstract of these studies.

AHRQ Review Concluded (September 2009[7]):

- Based on studies in participants requiring intensive lipid lowering therapy, there was very low quality of evidence demonstrating no difference in all cause mortality (14 trials; OR 0.61, 95% CI 0.22 to 1.71), no difference in vascular death (1 trial; OR 1.98, 95% CI 0.21 to 19.14) and a significant increase the number of participants reaching ATP III LDL-c goals in the combination group (18 trials; OR not pooled) between the combination of any dose statin plus ezetimibe and any dose statin monotherapy.
- Based on six studies in participants with established vascular disease, the evidence grade is “very low” showing no significant difference in all cause mortality (OR 0.66, 95% CI 0.19 to 2.31) and a significant increase in the number of participants reaching ATP III LDL-c goals favoring combination therapy (OR not pooled) between the combination of any dose statin plus ezetimibe and any dose statin monotherapy.
- Based on studies in participants regardless of baseline risk, the evidence grade is “very low” for no difference in all cause mortality (24 trials; OR 0.95, 95% CI 0.37 to 2.41), no difference in vascular death (2 trials; OR 2.70, 95% CI 0.38 to 19.2), no significant difference in serious adverse events (27 trials; OR 1.08, 95% CI 0.88 to 1.33) and a significant increase in the number of participants reaching ATP III LDL-c goals (23 trials; not pooled) between the combination of any dose statin plus ezetimibe and any dose statin monotherapy.

New Systematic Reviews:
There are no new systematic reviews evaluating the comparative effectiveness in long term cardiovascular outcomes. The only new systematic review published recently assessed the LDL lowering with the addition of ezetimibe to statin vs. statin titration in patients with hypercholesterolaemia.[36]

Conclusions:
Although ezetimibe acts on different pathway and has been shown to lower the LDL-C alone and in combination with a statin, it has not been shown to reduce long term cardiovascular clinical outcomes. Also, its safety has been questioned in a recent RCT.

Omega-3 Fatty Acids
Omega-3 fatty acids have been postulated to have a number of beneficial effects in patients at risk for vascular disease, including antithrombotic and blood pressure lowering effects. They are considered to be lipid lowering agents due to a reduction in triglycerides, particularly postprandially.[37-41] There are two forms of omega-3 fatty acids, eicosapentaenoic (EPA), dicisapentaenoic (DPA) and docosahexaenoic (DHA), and the plant oil derived alpha linolenic acid (ALA). Omega-3-acid reduces TG in patients with very high TG (>500mg/dl). American Heart Association (AHA) nutrition committee has recommended an intake of one gram of EPA + DHA per day for individuals with documented CHD and 2-4 grams per day for those needing to lower triglyverides.[42] Its efficacy in the secondary prevention of CVD remains inconclusive.

One large randomized open-label, blinded endpoint analysis, long term study was done in Japan by Yokoyama M.[43] The study enrolled total of 18,645 patients with a total cholesterol of 6.5 mmol/L (251mg/dL) or greater were recruited from local physicians throughout Japan between 1996 and 1999. Patients were randomly assigned to receive either 1,800 mg of EPA daily with a statin (EPA group; n=9,326) or a statin only (controls; n=9,319) with a 5-year follow-up. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. At mean follow-up of 4.6 years, study results showed the primary endpoint in 262 (2.8%) patients in the EPA group and 324 (3.5%) in controls, demonstrating a 0.7% absolute risk reduction in major coronary events (p=0.011). Unstable angina and non-fatal coronary events were also significantly reduced in the EPA group. Sudden cardiac death and coronary death did not differ between groups. In patients with a history of coronary artery disease who were given EPA treatment, major coronary events were reduced by 19% (secondary prevention subgroup: 158 [8.7%] in the EPA group vs. 197 [10.7%] in the control group; p=0.048). In patients with no history of coronary artery disease, EPA treatment reduced major coronary events by 18%, but this finding was not significant (104 [1.4%] in the EPA group vs. 127 [1.7%] in the control group; p=0.132). These results should be interpreted with caution due to its open label, poor study design.

AHRQ Review Concluded (September 2009[7]):

- Based on studies in participants regardless of baseline risk, the evidence grade is “very low” grade showing no significant difference in all cause mortality (3 trials; OR 1.08, 95% CI 0.91 to 1.28), and no significant difference serious adverse events (1 trial; OR 4.44, 95% CI 0.49 to 40.29) between the combination of any dose statin plus omega-3 and any dose statin monotherapy.
- No evidence was available to make conclusion regarding participants attainting the ATP III LDL goals or vascular death.
- Based on a single study in participants followed up for more than 24 weeks, the evidence grade is “very low” for no difference in all cause mortality (OR 1.08, 95% CI 0.91 to 1.28) between the combination of any dose statin plus omega-3 compared and any dose statin monotherapy.

New Systematic Reviews (Appendix B):
G.D. Eslick et al. published an updated the meta-analysis that included all placebo-controlled randomized trials of parallel design that evaluated any of the main blood lipid outcomes: total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol or triglycerides (TG).[44] Unfortunately this analysis did not examine the cardiovascular or stroke outcomes.

A recent meta-analysis investigated the efficacy of EPA and DPA in the secondary prevention of CVD including randomized, placebo-controlled trials.[45] The Jadad scale was used to assess the quality of each trial and of the fourteen RCTs included in the analysis, the mean Jadad score was 4.4 points for 7 trials using inappropriate randomization methods and 1 trial not describing the loss to follow-up. Results showed that omega-3 fatty acid supplementation did not reduce the risk of overall cardiovascular events (RR 0.99; 95% CI 0.89 to 1.09) and there were no significant differences in all cause mortality, sudden cardiac death, myocardial infarction, or stroke between the two groups. However, ometa-2 fatty acid supplementation did significantly reduce cardiovascular death (RR 0.91; 95% CI 0.84 – 0.99). A significant reduction was not seen when one trial was excluded that had a significant difference in the proportions with a history of angina between the two groups.

New Guideline:
There are no new guidelines published during this review period. However, American Heart Association AHA) published a scientific statement on Triglyceride and Cardiovascular disease in May 2011.[46] The statement stated "As monotherapy, fibrates offer the most TG reduction, followed by immediate-release niacin, omega-3 methyl esters, extended-release niacin, statins, and ezetimibe". It recommends 2 to 4 grams of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) per day for patients who need to lower their TG level.

Conclusions:
Omega fatty acids appear to have a role in cardiovascular risk factor management but the evidence base for therapeutic applications is still poorly defined. Although it is recommended by AHA for treatment of hypertriglyceridemia, several conflicting meta-analyses have failed to agree on the efficacy of taking fish oils for preventing cardiovascular disease or reducing cardiovascular mortality.[47 - 54] Omega fatty acid can be a treatment option for patients who have very high TG (>500 mg/dl) and failed or have contraindication to other triglyceride lowing agents.

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APPENDIX A: Previous Guidelines and Systematic Reviews:

Previous Guidelines

ATP III Update 2004[6]

- Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. TLC has the potential to reduce cardiovascular risk through several mechanisms beyond LDL lowering.
- In high-risk persons, the recommended LDL-C goal is < 100 mg/dL.
  - An LDL-C goal of < 70 mg/dL is a therapeutic option on the basis of available clinical trial evidence, especially for patients at very high risk.
  - If LDL-C is ≥ 100 mg/dL, an LDL-lowering drug is indicated simultaneously with lifestyle changes.
  - If baseline LDL-C is < 100 mg/dL, institution of an LDL-lowering drug to achieve an LDL-C level < 70 mg/dL is a therapeutic option on the basis of available clinical trial evidence.
  - If a high-risk person has high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. When triglycerides are ≥ 200 mg/dL, non-HDL-C is a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal.
- For moderately high-risk persons (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is < 130 mg/dL; an LDL-C goal _100 mg/dL is a therapeutic option on the basis of available clinical trial evidence. When LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level < 100 mg/dL is a therapeutic option on the basis of available clinical trial evidence.
- Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level.
- When LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.
- For people in lower-risk categories, recent clinical trials do not modify the goals and cutpoints of therapy.

ATP III Guidelines on Drug Therapy May 2001[3]

- Progression of drug therapy in primary prevention
  - Start statin or bile acid sequestrant or nicotinic acid
  - Consider higher dose of statin or add bile acid sequestrant or nicotinic acid
- Management of Specific Dyslipidemias
  - Very high LDL cholesterol (≥ 190mg/dL): often require combination drug therapy such as statin + bile acid sequestrant to achieve the LDL goal.
  - Elevated serum triglycerides:
    - Very high triglycerides (≥ 500mg/dL): TG lowering agent such as fibrate or nicotinic acid.
    - When lowered to < 500mg/dL: Intensify therapy with an LDL-lowering drug or add nicotinic acid or fibrate to achieve non-HDL cholesterol gaol.

Previous Systematic Review Conclusions (September 2009)[7]

❖ **Key Question 1. Long-Term Benefits and Serious Adverse Events**

- **All-cause mortality:** The quality of evidence was very low for all available comparisons of combinations and monotherapy reported. For individuals requiring intensive therapy, limited evidence was available for statin combinations with ezetimibe and fibrates compared to higher doses of statins.
- **Vascular death:** Treatments aimed at modifying lipids might be expected to lower the rates of death due to vascular diseases such as heart disease and stroke. However, no trials examined this outcome in a high-risk population and compared the combination to a higher statin dose.
- **Other clinical outcomes:** For the outcomes of reduction of MI or stroke or avoidance of revascularization procedures on the carotid or coronary vessels, no evidence comparing combination therapy with a higher dose of statin was available.
- **Serious adverse events:** The quality of evidence was very low for all available combination and monotherapy comparisons.
- **Cancer.** Evidence pertained to all available trial populations and not only those in need of intensive treatment. Some data were available for individuals at any risk level and statin dose.

❖ **Key Question 2. LDL-c Targets, Short-Term Side Effects, Tolerability, and Adherence**

- **Participants attaining ATP III LDL-c goals:** The available evidence is of very low quality for all comparisons of combination with monotherapy.
- **LDL-c:** When comparing a specific statin in combination with a higher dose statin in populations requiring intensive treatment, evidence was either insufficient or absent for statin-fibrate, statin-niacin, statin-BAS, and statin-omega-3 combinations.
- **HDL-c:** There is lack of evidence permitting meaningful conclusions from trials comparing a combination with higher dose of statin monotherapy in populations requiring intensive treatment.
- **Total cholesterol:HDL-c ratio:** When comparing a specific statin in combination with a higher dose statin in populations requiring intensive treatment, evidence was either absent or based on single-trial data, precluding robust conclusions across any combination therapy.
- **Measures of atherosclerosis:** Carotid intimal media thickness (IMT) can be measured by ultrasound and correlates with the presence of atherosclerotic plaque and vascular risk factors. Previous research has shown that statin treatment reduces the progression of this marker. Two trials were available that compared mean change from baseline in the IMT with combination therapy compared to statin monotherapy. Both trials yielded indeterminate results.
- **Adherence and harm:** For the comparison of a specific statin in combination with a higher dose of its monotherapy across all trial populations, insufficient evidence was available for all combinations except statin-ezetimibe, which showed no significant differences between treatments for the outcomes of withdrawal due to adverse events and liver toxicity (defined as AST/ALT above three times the upper limit of normal). Most trials had a short duration of treatment and follow up.

❖ **Key Question 3. Benefits and Harms Within Subgroups of Patients**

- **Participants with diabetes mellitus:** Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with a higher dose of statin monotherapy for any relevant outcomes.
- **Participants with established vascular disease:** Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with higher dose statin monotherapy for any relevant outcomes in individuals with pre-existing vascular disease.
- **Participants with baseline LDL-c of 190 mg/dL or above:** Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with higher dose statin monotherapy for any relevant outcomes.
- **Participants with cerebrovascular disease, females, participants of 80 years of age or older, participants of African descent, participants of Asian descent, and Hispanics:** No evidence was available for participants with cerebrovascular disease and those age 80 years and over. Sparse evidence of very low quality, precluding meaningful conclusions, was available in subgroups of participants of different ethnic origins and females.

APPENDIX B: Abstract of Systematic Reviews

1. A systematic review of bile acid sequestrant therapy in children with familial hypercholesterolemia Michael H. Davidson, MD, FACC, FACP, FNLA
The University of Chicago Pritzker School of Medicine, 515 North State Street, Suite 2700, Chicago, IL 60654, USA**.**
Journal of Clinical Lipidology 5, no. 2 (April 2011): 76–81.

   Abstract: Familial hypercholesterolemia, which arises as a result of a mutation in the low-density lipoprotein (LDL) receptor gene, is characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C), regardless of dietary and lifestyle modifications. Pharmacological therapy is often required to adequately control the elevated LDL-C levels associated with familial hypercholesterolemia. However, children with this genetic condition present many challenges for physicians, who must weigh the benefits of lipid-lowering therapy against the risks associated with the various treatment options. Furthermore, because familial hypercholesterolemia is a chronic condition, children will likely require long-term lipid-lowering therapy. As such, the potential effect of pharmacological treatment on development is of paramount importance in this population. Bile acid sequestrants represent a unique treatment option for children with familial hypercholesterolemia in that these agents are not systemically absorbed but rather exert their lipid-lowering effects via binding to bile acids within the gastrointestinal tract. A literature search was performed to identify clinical data related to the use of bile acid sequestrant therapy in children (,18 years of age) with familial hypercholesterolemia. Studies published in English between 1990 and December 2010 that were retrieved from MEDLINE and EMBASE were included in this systematic review. In total, five clinical studies were identified that evaluated bile acid sequestrant monotherapy, whereas two studies were identified that evaluated combination therapy with a bile acid sequestrant and low-dose statin. This review summarizes the clinical data regarding the efficacy and safety of bile acid sequestrants in this specialized population.

2. Efficacy offibratesforcardiovascularriskreductioninpersonswithatherogenic dyslipidemia: Ameta-analysis by Meng Lee a,b, JeffreyL.Savera,b, AmytisTowfighic, JessicaChowd, BruceOvbiagelee. Atherosclerosis (2011), doi:10.1016/j.atherosclerosis.2011.04.020

   Background: Recent datasuggestthatnon-targetedtreatmentwithfibratesmodestlyreducestheriskof incident cardiovascular events. However, the effect of fibrate treatment maybe particularly beneficial in patients with guideline-endorsed indications for therapy due to evidence of atherogenic dyslipidemia. We conducted a systematic review and meta-analysis to investigate the influence of fibrates on vascular risk reduction in persons with atherogenic dyslipidemia.

   Methods: Systematic search of Pub med, CENTRAL and recent reviews was conducted to identify atherogenic dyslipidemia (serum high density lipoprotein cholesterol [HDL-C]<40mg/dl or triglycerides >200mg/dl) cohorts from randomized controlled trials. RR with 95%CI was used as a measure of the association between fibrate therapy and risk of cardiovascular diseases, after pooling data across trials in a random-effects model.

   Results: Six trials met selection criteria. Compared to placebo, the greatest benefit with fibrate treatment was seen in 7,389 subjects with high triglycerides, fibrate therapy reduced risk of vascular events (RR 0.75, 95%CI0.65to0.86, P < 0.001); and in 5,068 subjects with both high triglycerides and low HDL-C (RR 0.71, 95%CI 0.62to0.82, P < 0.001). Less benefit was noted in 15,303 subjects selected for low HDL-C (RR 0.84, 95%CI 0.77to0.91, P <

0.001). Among 9872 subjects with neither high triglycerides nor low HDL-C, fibrate therapy did not reduce subsequent vascular events (RR0.96, 95%CI 0.85to1.09, P = 0.53).

Conclusions: Fibrate treatment directed at markers of atherogenic dyslipidemia substantially reduce subsequent vascular event risk.

3. Fibrates Effect on Cardiovascular Risk Is Greater in Patients With High Triglyceride Levels or Atherogenic Dyslipidemia Profile: A Systematic Review and Meta-analysis by Eric Bruckert, MD, PhD, Julien Labreuche, BS, Dominique Deplanque, MD, PhD, Pierre-Jean Touboul, MD, and Pierre Amarenco, MD. *Journal of Cardiovascular Pharmacology* 57, no. 2 (February 2011): 267–272.

   Abstract: According to recently published data, fibrates may reduce the risk of major cardiovascular events. Whether patients with low high-density lipoprotein cholesterol (HDL-C), high triglyceride levels, or both may have additional benefits remains under debate. We performed a meta-analysis of the 5 large trials assessing the impact of fibrates on cardiovascular end points and providing information on low HDL-C and high triglyceride levels. Subgroups were determined according to values closest to predetermined cut-offs for both HDL-C and triglycerides (35 and 200 mg/dL, respectively). Overall, 4,671 patients (2,401 in fibrate group and 2,270 in placebo group) were classified as having an atherogenic dyslipidemia featuring low HDLC combined with high triglyceride levels. Across trials, the proportion of patients classified in this subgroup ranged from 11% to 33%. We found a significant difference in the magnitude of fibrate effect across dyslipidemia subgroups (P for between-group heterogeneity = 0.0002). A greater effect size was found in patients with high triglyceride levels or atherogenic dyslipidemia phenotype where fibrates were estimated to reduce the cardiovascular risk by 28% [95% confidence interval (CI), 15% to 39%; P , 0.001] or 30% (95% CI, 19% to 40%, P , 0.0001), respectively, but only by 6% (95% CI, 22% to 13%, P = 0.13) in nonatherogenic dyslipidemia patients. Targeting patients with high triglyceride levels or atherogenic dyslipidemia with fibrates may help reduce residual vascular risk.

4. Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis by Eric Bruckerta, Julien Labreucheb,c, Pierre Amarenco. *Atherosclerosis* 210, no. 2 (June 2010): 353–361.

   Objective: High-density lipoprotein cholesterol (HDL-C) concentration is a strong predictor of cardiovascular events in both naïve and statin-treated patients. Nicotinic acid is an attractive option for decreasing residual risk in statin-treated or statin-intolerant patients since it increases HDL-C by up to 20% and decreases low-density lipoprotein cholesterol and lipoprotein(a) plasma concentrations.

   Methods: We performed a computerized Pub Med literature search that focused on clinical trials evaluating niacin, alone or in combination with other lipid-lowering drugs, published between January 1966 and August 2008.

   Results: Among 587 citations, 29 full articles were read and 14 were eligible for inclusion. Overall 11 randomized controlled trials enrolled 2682 patients in the active group and 3934 in the control group. In primary analysis, niacin significantly reduced major coronary events (relative odds reduction = 25%,

95% CI 13, 35), stroke (26%, 95% CI = 8, 41) and any cardiovascular events (27%, 95% CI = 15, 37). Except for stroke, the pooled between-group difference remained significant in sensitivity analysis excluding the largest trial. In comparison with the non-niacin group, more patients in the niacin group had regression of coronary atherosclerosis (relative increase = 92%, 95% CI = 39, 67) whereas the rate of patients with progression decreased by 41%, 95% CI = 25, 53. Similar effects of niacin were found on carotid intima thickness with a weighted mean difference in annual change of −17μm/year (95% CI =−22, −12).

Conclusions: Although the studies were conducted before statin therapy become standard care, and mostly in patients in secondary prevention, with various dosages of nicotinic acid 1–3 g/day, this meta-analysis found positive effects of niacin alone or in combination on all cardiovascular events and on atherosclerosis evolution.

5. Effect of Niacin Therapy on Cardiovascular Outcomes in Patients With Coronary Artery Disease by Jasleen K. Duggal, Mukesh Singh, Navneet Attri, Param P. Singh, Neyaz Ahmed, Suneet Pahwa, Janos Molnar, Sarabjeet Singh, Sandeep Khosla and Rohit Arora. *Journal of Cardiovascular Pharmacology and Therapeutics* 15(2) 158-166.

Background: Niacin or nicotinic acid (vitamin B3) raises the levels of high-density lipoprotein cholesterol (HDL) by about 30% to 35%. In patients with prior coronary disease, 7 trials have been published on clinical cardiovascular disease outcomes and the results, not surprisingly, are inconsistent. Hence, we performed this meta-analysis of randomized placebo-controlled trials (RCTs) to evaluate the effect of niacin on cardiovascular outcomes in patients with coronary artery disease.

Methods: A systematic search using PubMed, EMBASE, and Cochrane library databases was performed. Seven studies with a total of 5137 patients met our inclusion criteria. Heterogeneity of the studies was analyzed by the Cochran Q statistics. The significance of common treatment effect was assessed by computing the combined relative risks using the Mantel-Haenszel fixed-effect model. A 2-sided alpha error of less than .05 was considered statistically significant ($P < .05$).

Results: Compared to placebo group, niacin therapy significantly reduced coronary artery revascularization (RR [relative risk]: 0.307 with 95% CI: 0.150-0.628; $p = 0.001$), nonfatal myocardial infarction ([MI]; RR: 0.719; 95% CI: 0.603-0.856; $p = 0$ .000), stroke, and TIA ([transient ischemic attack] RR: 0.759; 95%CI: 0.613-0.940; $p = 0$ .012), as well as a possible but nonsignificant decrease in cardiac mortality (RR: 0.883: 95% CI: 0.773-1.008; $p = 0.066$).

6. Benefits of fish oil supplementation in hyperlipidemia: a systematic review and meta-analysis by Guy D. Eslick a,b, Peter R.C. Howe c, Caroline Smith a, Ros Priest a, Alan Bensoussan a. *International Journal of Cardiology* 136 (2009) 4–16.

Background: Fish oils have been widely reported as a useful supplement to reduce fasting blood triglyceride levels in individuals with hyperlipidemia. We performed an updated meta-analysis to quantitatively evaluate all the randomized trials of fish oils in hyperlipidemic subjects.

Methods: We conducted a systematic literature search using several electronic databases supplemented by manual searches of published reference lists, review articles and conference abstracts. We included all placebo-controlled randomized trials of parallel design that evaluated any of the main blood lipid outcomes: total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol or triglycerides (TG). Data were pooled using DerSimonian–Laird's random effects model.

Results: The final analysis comprised of 47 studies in otherwise untreated subjects showed that taking fish oils (weighted average daily intake of 3.25 g of EPA and/or DHA) produced a clinically significant reduction of TG (−0.34 mmol/L, 95% CI: −0.41 to −0.27), no change in total cholesterol (−0.01 mmol/L, 95% CI: −0.03 to 0.01) and very slight increases in HDL (0.01 mmol/L, 95% CI: 0.00 to 0.02) and LDL cholesterol (0.06 mmol/L, 95% CI: 0.03 to 0.09). The reduction of TG correlated with both EPA+DHA intake and initial TG level.

Conclusion: Fish oil supplementation produces a clinically significant dose-dependent reduction of fasting blood TG but not total, HDL or LDL cholesterol in hyperlipidemic subjects.

7. Kwak SM, Myung SK, Lee YJ, Seo HG; for the Korean Meta-analysis Study Group. Efficacy of Omega-3 Fatty Acid Supplements (Eicosapentaenoic Acid and Docosahexaenoic Acid) in the Secondary Prevention of Cardiovascular Disease: A Meta-analysis of Randomized, Double-blind, Placebo-Controlled Trials. Arch Intern Med. 2012 Apr 9. [Epub ahead of print]

   Background: Although previous randomized, double-blind, placebo-controlled trials reported the efficacy of omega-3 fatty acid supplements in the secondary prevention of cardiovascular disease (CVD), the evidence remains inconclusive. Using a meta-analysis, we investigated the efficacy of eicosapentaenoic acid and docosahexaenoic acid in the secondary prevention of CVD.

   Methods:We searched PubMed, EMBASE, and the Cochrane Library in April 2011. Two of us independently reviewed and selected eligible randomized controlled trials.

   Results: Of 1007 articles retrieved, 14 randomized, double-blind, placebo-controlled trials (involving 20 485 patients with a history of CVD) were included in the final analyses. Supplementation with omega-3 fatty acids did not reduce the risk of overall cardiovascular events (relative risk, 0.99; 95% CI, 0.89-1.09), all-cause mortality, sudden cardiac death, myocardial infarction, congestive heart failure, or transient ischemic attack and stroke. There was a small reduction in cardiovascular death (relative risk, 0.91; 95% CI, 0.84-0.99), which disappeared when we excluded a study with major methodological problems. Furthermore, no significant preventive effect was observed in subgroup analyses by the following: country location, inland or coastal geographic area, history of CVD, concomitant medication use, type of placebo material in the trial, methodological quality of the trial, duration of treatment, dosage of eicosapentaenoic acid or docosahexaenoic acid, or use of fish oil supplementation only as treatment.

Conclusion: Our meta-analysis showed insufficient evidence of a secondary preventive effect of omega-3 fatty acid supplements against overall cardiovascular events among patients with a history of cardiovascular disease.

APPENDIX C: Selected Abstract of RTCs

1. **Simvastatin with or without ezetimibe in familial hypercholesterolemia.**

Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, Visseren FL, Sijbrands EJ, Trip MD, Stein EA, Gaudet D, Duivenvoorden R, Veltri EP, Marais AD, de Groot E; ENHANCE Investigators. Collaborators (13)
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Erratum in N Engl J Med. 2008 May 1;358(18):1977.

Abstract

BACKGROUND: Ezetimibe, a cholesterol-absorption inhibitor, reduces levels of low-density lipoprotein (LDL) cholesterol when added to statin treatment. However, the effect of ezetimibe on the progression of atherosclerosis remains unknown.

METHODS: We conducted a double-blind, randomized, 24-month trial comparing the effects of daily therapy with 80 mg of simvastatin either with placebo or with 10 mg of ezetimibe in 720 patients with familial hypercholesterolemia. Patients underwent B-mode ultrasonography to assess the intima-media thickness of the walls of the carotid and femoral arteries. The primary outcome measure was the change in the mean carotid-artery intima-media thickness, which was defined as the average of the means of the far-wall intima-media thickness of the right and left common carotid arteries, carotid bulbs, and internal carotid arteries.

RESULTS: The primary outcome, the mean (+/-SE) change in the carotid-artery intima-media thickness, was 0.0058+/-0.0037 mm in the simvastatin-only group and 0.0111+/-0.0038 mm in the simvastatin-plus-ezetimibe (combined-therapy) group (P=0.29). Secondary outcomes (consisting of other variables regarding the intima-media thickness of the carotid and femoral arteries) did not differ significantly between the two groups. At the end of the study, the mean (+/-SD) LDL cholesterol level was 192.7+/-60.3 mg per deciliter (4.98+/-1.56 mmol per liter) in the simvastatin group and 141.3+/-52.6 mg per deciliter (3.65+/-1.36 mmol per liter) in the combined-therapy group (a between-group difference of 16.5%, P<0.01). The differences between the two groups in reductions in levels of triglycerides and C-reactive protein were 6.6% and 25.7%, respectively, with greater reductions in the combined-therapy group (P<0.01 for both comparisons). Side-effect and safety profiles were similar in the two groups.

CONCLUSIONS: In patients with familial hypercholesterolemia, combined therapy with ezetimibe and simvastatin did not result in a significant difference in changes in intima-media thickness, as compared with simvastatin alone, despite decreases in levels of LDL cholesterol and C-reactive protein. ***(ClinicalTrials.gov number, NCT00552097 [ClinicalTrials.gov].).***

2. **The ARBITER 6-HALTS Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis): final results and the impact of medication adherence, dose, and treatment duration.**

Villines TC, Stanek EJ, Devine PJ, Turco M, Miller M, Weissman NJ, Griffen L, Taylor AJ.

Source: Cardiology Service, Walter Reed Army Medical Center, Washington, DC 20307, USA. todd.villines@amedd.army.mil

Abstract

OBJECTIVES: This report describes the final results of the ARBITER 6-HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis) trial.

BACKGROUND: The ARBITER 6-HALTS trial was terminated early on the basis of a pre-specified interim analysis showing superiority of niacin over ezetimibe on change in carotid intima-media thickness (CIMT). After termination, an additional 107 subjects completed a close-out assessment.

METHODS: Patients with coronary heart disease (CHD) or CHD equivalent with low-density lipoprotein cholesterol <100 mg/dl and high-density lipoprotein cholesterol <50 mg/dl for men or 55 mg/dl for women while receiving stable statin treatment were randomly assigned to ezetimibe (10 mg/day) or extended-release niacin (target dose, 2,000 mg/day). The primary end point was change in mean CIMT, analyzed according to a last observation carried forward method. The relationships of study medication adherence, dosage, and cumulative exposure (product of adherence, dose, and time) with change in CIMT were explored.

RESULTS: Results in 315 patients included 208 with 14-month follow-up and 107 after mean treatment of 7 +/- 3 months. Niacin (n = 154) resulted in significant reduction (regression) in mean CIMT (-0.0102 +/- 0.0026 mm; p < 0.001) and maximal CIMT (-0.0124 +/- 0.0036 mm; p = 0.001), whereas ezetimibe (n = 161) did not reduce mean CIMT (-0.0016 +/- 0.0024 mm; p = 0.88) or maximal CIMT (-0.0005 +/- 0.0029 mm; p = 0.88) compared with baseline. There was a significant difference between ezetimibe and niacin treatment groups on mean changes in CIMT, favoring niacin, for both mean CIMT (p = 0.016) and maximal CIMT (p = 0.01). Increased cumulative drug exposure was related to regression of CIMT with niacin, and progression of CIMT with ezetimibe.

CONCLUSIONS: Niacin induces regression of CIMT and is superior to ezetimibe for patients taking statins. (Comparative Study of the Effect of Ezetimibe Versus Extended-Release Niacin on Atherosclerosis; NCT00397657).

3. **Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis.**

Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, Gerdts E, Gohlke-Bärwolf C, Holme I, Kesäniemi YA, Malbecq W, Nienaber CA, Ray S, Skjaerpe T, Wachtell K, Willenheimer R; SEAS Investigators. Collaborators (445) Source:Division of Cardiology, Aker University Hospital, Trondheimsveien 235, N-0514 Oslo, Norway. anne@rossebo.net

Abstract

BACKGROUND: Hyperlipidemia has been suggested as a risk factor for stenosis of the aortic valve, but lipid-lowering studies have had conflicting results.

METHODS: We conducted a randomized, double-blind trial involving 1873 patients with mild-to-moderate, asymptomatic aortic stenosis. The patients received either 40 mg of simvastatin plus 10 mg of ezetimibe or placebo daily. The primary outcome was a composite of major cardiovascular events, including death from cardiovascular causes, aortic-valve replacement, nonfatal myocardial infarction, hospitalization for unstable angina pectoris, heart failure, coronary-artery bypass grafting, percutaneous coronary intervention, and nonhemorrhagic stroke. Secondary outcomes were events related to aortic-valve stenosis and ischemic cardiovascular events.

RESULTS: During a median follow-up of 52.2 months, the primary outcome occurred in 333 patients (35.3%) in the simvastatin-ezetimibe group and in 355 patients (38.2%) in the placebo group (hazard ratio in the simvastatin-ezetimibe group, 0.96; 95% confidence interval [CI], 0.83 to 1.12; P=0.59). Aortic-valve replacement was performed in 267 patients (28.3%) in the simvastatin-ezetimibe group and in 278 patients (29.9%) in the placebo group (hazard ratio, 1.00; 95% CI, 0.84 to 1.18; P=0.97). Fewer patients had ischemic cardiovascular events in the simvastatin-ezetimibe group (148 patients) than in the placebo group (187 patients) (hazard ratio, 0.78; 95% CI, 0.63 to 0.97; P=0.02), mainly because of the smaller number of patients who underwent coronary-artery bypass grafting. Cancer occurred more frequently in the simvastatin-ezetimibe group (105 vs. 70, P=0.01).

CONCLUSIONS: Simvastatin and ezetimibe did not reduce the composite outcome of combined aortic-valve events and ischemic events in patients with aortic stenosis. Such therapy reduced the incidence of ischemic cardiovascular events but not events related to aortic-valve stenosis. (ClinicalTrials.gov number, NCT00092677.)