Published in final edited form as:
Am J Cardiol. 2008 October 15; 102(8): 1040–1045. doi:10.1016/j.amjcard.2008.05.056.

Effectiveness of Combined Statin Plus Omega-3 Fatty Acid Therapy for Mixed Dyslipidemia

Philip Barter, MD, PhD[a] and **Henry N. Ginsberg, MD**[b,*]

[a]Heart Research Institute, Camperdown, Sydney, New South Wales, Australia;

[b]Irving Institute for Clinical and Translational Research, Columbia University, New York, New York.

Abstract

Combination therapy for the treatment of dyslipidemia and reduction of cardiovascular risk has been demonstrated to beneficially modify the lipid profile in multiple randomized clinical trials. As reported in the updated National Cholesterol Education Program Adult Treatment Panel III guidelines, low-density lipoprotein (LDL) cholesterol remains the primary treatment target, although the comprehensive management of dyslipidemia in high-risk patients includes the modification of secondary lipid parameters such as triglycerides, high-density lipoprotein cholesterol, and non–high-density lipoprotein cholesterol. Although statin therapy is the standard intervention for lowering LDL cholesterol, combination therapy has demonstrated added benefits on secondary lipid parameters and enhances statin-mediated reductions in LDL cholesterol. The benefits of modifying these secondary targets on all-cause or cardiovascular event–related mortality are currently under investigation in several clinical trials. Prescription omega-3 fatty acid (Lovaza) is a formulation of 2 highly purified omega-3-acid ethyl esters, eicosapentaenoic acid and docosahexaenoic acid. The recently completed Combination of Prescription Omega-3 With Simvastatin (COMBOS) study confirmed that prescription omega-3 fatty acid administered in combination with simvastatin achieves statistically significant improvements across a range of lipid indicators beyond the LDL primary target, including triglycerides, non–high-density lipoprotein cholesterol, and lipoprotein particle size. In conclusion, several classes of drugs, including omega-3 fatty acids, can be used in combination with statins to achieve more global improvements in lipid profiles.

On the basis of large outcome trials with statins, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines recommend reducing low-density lipoprotein (LDL) cholesterol to a goal of 100 mg/dl in high-risk patients and 70 mg/dl in very high risk patients.[1–6] Clinical experiences confirm that a substantial proportion of patients do not achieve target LDL cholesterol levels with initial statin monotherapy.[7,8]

Recent ATP III guidelines acknowledged the importance of secondary targets for therapy in dyslipidemic patients.[1] The level of non–high-density lipoprotein (HDL) cholesterol (calculated by subtracting HDL cholesterol from total cholesterol) is an indicator of future cardiovascular events,[9–11] and in patients with hypertriglyceridemia, lowering non-HDL cholesterol and triglycerides may further reduce cardiovascular risk.[1] The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction (PROVE IT–TIMI 22) trial recently showed that an on-treatment triglyceride level <150 mg/

*Corresponding author: Tel: 212-305-9562; fax: 212-305-3213. hng1@columbia.edu. .

dl was independently associated with a significant reduction in risk for recurrent coronary artery disease events, including recurrent acute coronary syndromes, myocardial infarction, and death.12

High-risk patients with combined dyslipidemia represent a major treatment dilemma because they are often statin-treated individuals who may or may not have attained ATP III threshold goals for LDL cholesterol, yet they remain at high risk for future cardiovascular events because of persistent hypertriglyceridemia and elevated non-HDL cholesterol levels. In the NCEP Evaluation Project Utilizing Novel E-Technology (NEPTUNE) II survey, the percentages of patients with high triglycerides (>200 mg/dl) who reached LDL cholesterol and non-HDL cholesterol ATP III treatment goals were 64%, 52%, and 27%, respectively, for groups with 0 or 1 risk factor, ≥2 risk factors, or coronary artery disease.[13] Thus, the addition of a second or third agent is an important therapeutic consideration for these patients. In this review, we discuss the rationale, clinical experience, and safety of omega-3 fatty acid (OM3-FA) and statin combination therapy as a therapeutic option for managing mixed dyslipidemia.

Statin Combination with Colesevelam, Ezetimibe, Niacin, or Fibrate

Statin combination therapy is often necessary for reaching the more aggressive LDL cholesterol and secondary (HDL cholesterol, non-HDL cholesterol, and triglyceride) goals recommended as treatment targets for high-risk patients with combined or mixed hyperlipidemia.[1,14] Depending on a patient's specific hyperlipidemic profile and sensitivities, combination therapies may include a bile acid sequestrant, ezetimibe, niacin, fibrates, or OM3-FAs in addition to statin treatment. What follows is a brief review of agents most frequently used for combination therapy with statins.

Colesevelam, a nonabsorbed hydrogel, is a second-generation bile acid–binding resin that has higher affinity and greater specificity for bile acids than cholestyramine or colestipol. Colesevelam can further significantly reduce LDL cholesterol levels when used in combination with a statin (10% to 25%). Treatment with colesevelam is well tolerated and associated with no significant adverse events.[15] Combinations of ezetimibe and a statin have additive effects on LDL cholesterol reduction, with a 7% to 20% further decrease over statins alone.16 This is an effective drug combination for patients who cannot tolerate higher statin doses, with the most common side effects being nausea and transaminase elevations.[16,17] In general, neither colesevelam nor ezetimibe has significant effects on triglycerides or HDL cholesterol.

In combination with statin, niacin further reduces LDL cholesterol (10% to 20%), non-HDL cholesterol, and triglycerides (10% to 30%) and increases HDL cholesterol (20% to 40%). However, many patients have difficulty tolerating niacin because of relatively benign but trouble-some adverse events, namely, flushing. Flushing persists, although less frequently, even with some of the newer extended-release formulations. Doses >2,000 mg/day in combination with a statin should be avoided because of the potential for myopathy.[14,18,19]

Fibrate-statin combinations produce significant additional decreases in triglycerides (30% to 50%) and increases in HDL cholesterol (10% to 20%) in comparison with statin monotherapy.[14,20] Patients should be closely monitored for myopathy when given fibrates and statins in combination. However, the addition of fenofibrate to statin therapy does not appear to increase myopathy significantly, possibly because fenofibrate does not increase blood levels of statins.21

Omega-3 Fatty Acids in the Treatment of Dyslipidemia

OM3-FAs, including eicosapentaenoic acid and docosahexaenoic acid, are typically found in fish oil.[22] OM3-FAs exert a dose-dependent decrease on serum triglycerides that is most apparent in subjects with greater baseline triglyceride levels. Observational and clinical trial data suggest OM3-FA can reduce the risk for coronary artery disease–related death,23،24 reduce nonfatal coronary events,25 and suppress cardiac arrhythmias.[26] In a meta-analysis of OM3-FAs as supplements or dietary components, there was a significant reduction in triglycerides of −27 mg/dl (95% confidence interval −33 to −20), a significant increase in HDL cholesterol of 2 mg/dl (95% confidence interval 1 to 2), and a significant increase of in LDL cholesterol 6 mg/dl (95% confidence interval 3 to 8) (Figure 1).[27] Clinical experience with OM3-FA suggests that it is well tolerated, with few adverse effects other than taste perversion and eructation. Treatment has not been associated with hyperglycemia, rhabdomyolysis, hepatic or renal impairment, or bleeding disorders, and no safety concerns requiring special patient surveillance have been identified.[28] Several studies have demonstrated the safety and efficacy of a statin plus OM3-FA.

After an initial study period of 6 weeks comparing pravastatin 40 mg/day with fish oil 6 g/day or placebo, subjects from the placebo group were administered pravastatin and fish oil for 12 weeks. Aside from nausea, no treatment-related adverse events were reported, and the combination reduced the concentration of very low density lipoprotein (VLDL) cholesterol and intermediate-density lipoprotein cholesterol by 35% and the total cholesterol/triglycerides ratio in VLDL cholesterol by 25%.[29]

In a study looking at the dose-dependent effects of docosahexaenoic acid supplementation in 45 statin-treated subjects with hyperlipidemia taking either 4 or 8 g/day of tuna oil or olive oil (placebo), a dose-dependent 27% reduction in triglycerides was observed with 8 g/day docosahexaenoic acid–rich fish oil by 3 months; this change was sustained at 6 months. Total cholesterol reductions were correlated with initial cholesterol levels, and fish oil tended to lower cholesterol and apolipoprotein B levels within VLDL cholesterol.[30]

The Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS) was designed to study the effects of eicosapentaenoic acid on major coronary events in patients with hypercholesterolemia.[25] A total of 18,645 patients were randomized to receive either 1,800 mg of eicosapentaenoic acid plus statin or statin alone. LDL cholesterol was reduced by 25% in the 2 groups. Triglyceride levels were unchanged during the trial. This study reported a 19% relative reduction in the primary end point of major coronary events. Unstable angina and nonfatal coronary events were also reduced in the eicosapentaenoic acid study group. Although this trial showed a reduction in coronary events, it was not designed as a double-blind study. To date, this is the only study to show a significant reduction in coronary events from combination treatment with OM3-FA or prescription OM3-FA (P-OM3) and a statin.

Statin Plus Prescription Omega-3 Fatty Acid Combination Studies

OM3-FAs have been highly purified in a prescription formulation (Lovaza; GlaxoSmithKline, Beecham, North Carolina), which contains 465 mg eicosapentaenoic acid, 375 mg docosahexaenoic acid, and 6 IU vitamin E in each 1-g capsule. (Reliant Pharmaceuticals, Liberty Corner, New Jersey, a subsidiary of GlaxoSmithKline, has changed the name of Omacor [omega-3-acid ethyl esters] to Lovaza at the request of the United States Food and Drug Administration in response to a limited number of reports of prescribing and dispensing errors[31] due to similarities in name between Omacor and Amicar [aminocaproic acid; Xanodyne Pharmaceuticals, Florence, Kentucky]. The name change is intended to minimize the potential for such errors in the future. The prescribing information

has been updated to reflect the new name, and new clinical data have been added to the label.) P-OM3 is the most highly purified form of OM3-FA and is the only formulation currently approved by the United States Food and Drug Administration for patients with hypertriglyceridemia (triglycerides >500 mg/dl). The results of clinical trials on the combination of P-OM3 and a statin, including the recent Combination of Prescription Omega-3 With Simvastatin (COMBOS) trial that looked specifically at patients with hypertriglyceridemia, and in which non-HDL cholesterol was the primary end point, are discussed later.

When simvastatin (20 mg/day) was administered as monotherapy, as well as in combination with P-OM3 (4 g/day) in 41 combined patients with dyslipidemia, the addition of P-OM3 was associated with significant reductions in serum triglyceride ($p = 0.007$) and apolipoprotein E ($p = 0.035$) levels and a borderline significant decrease in total cholesterol ($p = 0.052$) concentration over the course of a 5-week treatment interval.[32] The P-OM3–mediated decrease in triglycerides and total cholesterol was observed without an undesirable increase in LDL cholesterol in this study, presumably because of the concurrent inhibition of cholesterol synthesis by simvastatin.

In that same study population,[33] supplementation with P-OM3 reduced fasting levels of tissue factor pathway inhibitor antigen ($p < 0.05$), the degree of postprandial hyperlipidemia ($p < 0.005$), and the concentration of activated factor VII during postprandial hyperlipidemia. These findings indicated that combination therapy involving simvastatin and high doses of P-OM3 may reduce the thrombotic potential in patients with combined hyperlipidemia and at the same time reduce the concentration of atherogenic lipoproteins.

The efficacy, safety, and tolerability of P-OM3 (4 g/day) administered for ≥1 year to high-risk patients as an adjunct to preexisting simvastatin therapy (10 to 40 mg/day) were evaluated in a randomized, placebo-controlled study enrolling 59 patients with established coronary artery disease.[34] All patients had serum triglycerides >200 mg/dl at entry. Participants were randomly assigned to P-OM3 (2 g twice daily) or placebo for 24 weeks in a double-blind initial phase, with 46 subjects continuing active treatment for an additional 24 weeks in a subsequent open phase. Patients receiving P-OM3 and simvastatin demonstrated a sustained, significant 20% to 30% decrease in serum triglycerides ($p < 0.005$) and a significant 30% to 40% decrease in VLDL cholesterol ($p < 0.005$) compared with those receiving simvastatin alone. Treatment effects were statistically significant by 12 weeks and were sustained for the full 12-month duration of the trial. P-OM3 therapy exerted no undesirable effects on LDL cholesterol and no adverse effects on glycemic control in patients with diabetes.34

Atorvastatin and P-OM3 were found to exert independent, synergistic improvements in serum lipid profiles in middle-aged, viscerally obese men (mean body mass index 34 ± 0.6 kg/m^2) with dyslipidemia and insulin resistance.[35] Treatment combinations were specified in accord with a 2×2 matrix to allow for the identification of treatment effects associated with the various medications alone, in combination, and compared with placebo. In this 6-week, randomized, placebo-controlled intervention study, the combination of atorvastatin (40 mg/day) and P-OM3 (4 g/day) achieved significant treatment effects across a range of lipid parameters, with each component contributing clearly different benefits. Atorvastatin significantly decreased triglycerides (-34 ± 1.8 mg/dl, $p = 0.002$), total cholesterol (-73 ± 6.6 mg/dl, $p = 0.001$), LDL cholesterol (-69 ± 5.4 mg/dl, $p = 0.001$), remnant-like particle cholesterol (-3.1 ± 1.5 mg/dl, $p = 0.035$), apolipoprotein B (-49 ± 4 mg/dl, $p = 0.001$), and apolipoprotein C-III (-13 ± 6.1 mg/L, $p = 0.044$) and significantly increased HDL cholesterol (3.9 ± 1.6 mg/dl, $p = 0.007$). P-OM3 supplementation significantly reduced

triglycerides (−34 ± 9.8 mg/dl, p = 0.002) and was associated with significant increases in HDL cholesterol (2.7 ± 1.6 mg/dl, p = 0.041).[35]

The COMBOS trial evaluated the efficacy of P-OM3 added to stable statin therapy in subjects with persistent hypertriglyceridemia. Importantly, this was the largest trial to specifically investigate the effect of P-OM3 supplementation on levels of non-HDL cholesterol. Investigators at multiple sites enrolled 254 adults, all of whom had been receiving statin treatment for ≥8 weeks, with fasting triglyceride levels of 200 to 499 mg/dl and LDL cholesterol fractions ≤10% within their NCEP ATP III goal.[36] All participants received simvastatin 40 mg without dosage modification for the duration of the study. The primary outcome variable was the percentage change from baseline to the end of treatment in non-HDL cholesterol. Secondary outcome variables included, but were not limited to, percentage changes from baseline to the end of treatment in the levels of triglycerides, VLDL cholesterol, LDL cholesterol, and HDL cholesterol.[36]

Non-HDL cholesterol was significantly lower after treatment with P-OM3 plus simvastatin compared with treatment with placebo plus simvastatin (−9.0% vs −2.2%, respectively). In subjects treated with P-OM3 who had increased non-HDL cholesterol levels at baseline, >50% were able to attain non-HDL cholesterol goals by the end of treatment, nearly twice the rate of those attaining treatment goals among placebo-treated subjects.[36] P-OM3 therapy in combination with simvastatin was associated with substantial reductions in triglycerides, achieving a median decrease of 30% in comparison with a median decrease of 6.3% in the group receiving placebo and simvastatin. Median decreases in VLDL cholesterol were significantly greater with treatment with P-OM3 and simvastatin compared with placebo and simvastatin (28% and 7.2%, respectively). LDL cholesterol increased by a median of 0.7% with P-OM3 and simvastatin, insignificantly different from a median decrease of 2.8% documented for placebo and simvastatin. HDL cholesterol increased by a median of 3.4% with P-OM3 and simvastatin, in contrast to a median decrease of 1.2% in subjects receiving simvastatin monotherapy (Table 1). No significant differences in adverse events were reported.

Summary

The use of multiple agents is commonplace and readily accepted for the management of hypertension and diabetes, but the prevalence of combination treatment for dyslipidemia, an enormous and expanding health care problem, has not substantially changed from more than a decade ago.[9] It remains an underused clinical strategy despite expert consensus on its efficacy and tolerability.

There are no current data from a randomized, double-blind trial that support the addition of any OM3-FA to statin therapy for reducing future cardiovascular events. Although the large JELIS trial showed a significant reduction in cardiovascular events in patients receiving combination therapy with OM3-FA and a statin, that study was not double blinded.[25] The addition of OM3-FA, specifically P-OM3, is approved and recommended for reducing triglycerides in patients with hypertriglyceridemia (triglycerides >500 mg/dl). In addition, accumulating clinical trial data suggest that P-OM3 significantly reduces non-HDL cholesterol, a recognized and possibly more important predictor of future cardiovascular events than LDL cholesterol alone.[11,37]

The most recent ATP III guidelines included non-HDL cholesterol as a secondary target in the management of dyslipidemia in patients with high triglycerides. The COMBOS trial confirmed that P-OM3 administered in a combination statin regimen significantly lowered serum triglycerides across a range of non-HDL cholesterol lipid parameters.[36] This combination represents a therapeutic option for these patients in whom NCEP ATP III goals

are unachievable with monotherapy and/or other combination strategies. With a low incidence of adverse events, combination therapy with P-OM3 and a statin warrants consideration as a therapy for patients with combined dyslipidemia and persistent hypertriglyceridemia.

Acknowledgments

We acknowledge DesignWrite, LLC (Princeton, New Jersey), for their contribution to the initial draft of this report on the basis of our scientific and medical direction. The report was extensively reviewed and revised by the authors.

This report was funded in part by Reliant Pharmaceuticals, Liberty Corner, New Jersey, a subsidiary of GlaxoSmithKline, Beecham, North Carolina.

References

1. Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–3421. [PubMed: 12485966]
2. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227–239. [PubMed: 15249516]
3. Jacobson TA. The safety of aggressive statin therapy: how much can low-density lipoprotein cholesterol be lowered? Mayo Clin Proc 2006;81:1225–1231. [PubMed: 16970219]
4. Wiviott SD, Cannon CP, Morrow DA, Ray KK, Pfeffer MA, Braunwald E. Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy: a PROVE IT-TIMI 22 substudy. J Am Coll Cardiol 2005;46:1411–1416. [PubMed: 16226163]
5. McKenney JM, Jones PH, Adamczyk MA, Cain VA, Bryzinski BS, Blasetto JW. Comparison of the efficacy of rosuvastatin versus atorvastatin, simvastatin, and pravastatin in achieving lipid goals: results from the STELLAR trial. Curr Med Res Opin 2003;19:689–698. [PubMed: 14687438]
6. Ballantyne CM, Bertolami M, Garcia HR Hernandez, Nul D, Stein EA, Theroux P, Weiss R, Cain VA, Raichlen JS. Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY) II. Am Heart J 2006;151:975–979. [PubMed: 16644314]
7. Pearson TA, Laurora I, Chu H, Kafonek S. The Lipid Treatment Assessment Project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. Arch Intern Med 2000;160:459–467. [PubMed: 10695686]
8. Schuster H. Improving lipid management—to titrate, combine or switch. Int J Clin Pract 2004;58:689–694. [PubMed: 15311726]
9. Maki KC, Galant R, Davidson MH. Non-high-density lipoprotein cholesterol: the forgotten therapeutic target. Am J Cardiol 2005;96:59K–64K.
10. Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. Circulation 2005;112:3375–3383. [PubMed: 16316964]
11. Miller M, Ginsberg HN, Schaefer EJ. Relative atherogenicity and predictive value of non-high-density lipoprotein cholesterol for coronary heart disease. Am J Cardiol 2008;101:1003–1008. [PubMed: 18359322]
12. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2008;51:724–730. [PubMed: 18279736]
13. Davidson MH, Maki KC, Pearson TA, Pasternak RC, Deedwania PC, McKenney JM, Fonarow GC, Maron DJ, Ansell BJ, Clark LT, Ballantyne CM. Results of the National Cholesterol

Education (NCEP) Program Evaluation Project Utilizing Novel E-Technology (NEPTUNE) II survey and implications for treatment under the recent NCEP Writing Group recommendations. Am J Cardiol 2005;96:556–563. [PubMed: 16098311]

14. Goldberg AC. Combination therapy of dyslipidemia. Curr Treat Options Cardiovasc Med 2007;9:249–258. [PubMed: 17761110]
15. Hunninghake D, Insull W Jr, Toth P, Davidson D, Donovan J, Burke S. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. Atherosclerosis 2001;158:407–416. [PubMed: 11583720]
16. Bays HE, Ose L, Fraser N, Tribble DL, Quinto K, Reyes R, Johnson-Levonas AO, Sapre A, Donahue SR. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clin Ther 2004;26:1758–1773. [PubMed: 15639688]
17. Ballantyne CM, Weiss R, Moccetti T, Vogt A, Eber B, Sosef F, Duffield E. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). Am J Cardiol 2007;99:673–680. [PubMed: 17317370]
18. Brown BG, Zhao X-Q, Chait A, Fisher LD, Cheung MC, Morse JS, Dowdy AA, Marino EK, Bolson EL, Alaupovic P, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med 2001;345:1583–1592. [PubMed: 11757504]
19. Kashyap ML, McGovern ME, Berra K, Guyton JR, Kwiterovich PO, Harper WL, Toth PD, Favrot LK, Kerzner B, Nash SD, et al. Longterm safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia. Am J Cardiol 2002;89:672–678. [PubMed: 11897208]
20. Grundy SM, Vega GL, Yuan Z, Battisti WP, Brady WE, Palmisano J. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). Am J Cardiol 2005;95:462–468. [PubMed: 15695129]
21. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. Am J Cardiol 2005;95:120–122. [PubMed: 15619408]
22. Harris WS. Omega-3 fatty acids and cardiovascular disease: a case for omega-3 index as a new risk factor. Pharmacol Res 2007;55:217–223. [PubMed: 17324586]
23. Psota TL, Gebauer SK, Kris-Etherton P. Dietary omega-3 fatty acid intake and cardiovascular risk. Am J Cardiol 2006;98:3I–18I.
24. Jacobson TA. Secondary prevention of coronary artery disease with omega-3 fatty acids. Am J Cardiol 2006;98:61I–70I.
25. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007;369:1090–1098. [PubMed: 17398308]
26. Leaf A. Omega-3 fatty acids and prevention of arrhythmias. Curr Opin Lipidol 2007;18:31–34. [PubMed: 17218829]
27. Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. Atherosclerosis 2006;189:19–30. [PubMed: 16530201]
28. McKenney JM, Sica D. Prescription omega-3 fatty acids for the treatment of hypertriglyceridemia. Am J Health Syst Pharm 2007;64:595–605. [PubMed: 17353568]
29. Contacos C, Barter PJ, Sullivan DR. Effect of pravastatin and omega-3 fatty acids on plasma lipids and lipoproteins in patients with combined hyperlipidemia. Arterioscler Thromb 1993;13:1755–1762. [PubMed: 8241095]
30. Meyer BJ, Hammervold T, Rustan AC, Howe PR. Dose-dependent effects of docosahexaenoic acid supplementation on blood lipids in statin-treated hyperlipidaemic subjects. Lipids 2007;42:109–115. [PubMed: 17393216]
31. Reliant Pharmaceuticals, Inc.. Reliant Pharmaceuticals; Liberty Corner, New Jersey: 2008. Press releaseAvailable at

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

32. Nordoy A, Bonaa KH, Nilsen H, Berge RK, Hansen JB, Ingebretsen OC. Effects of simvastatin and omega-3 fatty acids on plasma lipoproteins and lipid peroxidation in patients with combined hyperlipidaemia. J Intern Med 1998;243:163–170. [PubMed: 9566646]
33. Nordoy A, Bonaa KH, Sandset PM, Hansen JB, Nilsen H. Effect of omega-3 fatty acids and simvastatin on hemostatic risk factors and postprandial hyperlipemia in patients with combined hyperlipemia. Arterioscler Thromb Vasc Biol 2000;20:259–265. [PubMed: 10634827]
34. Durrington PN, Bhatnagar D, Mackness MI, Morgan J, Julier K, Khan MA, France M. An omega-3 polyunsaturated fatty acid concentrate administered for one year decreased triglycerides in simvastatin treated patients with coronary heart disease and persisting hypertriglyceridaemia. Heart 2001;85:544–548. [PubMed: 11303007]
35. Chan DC, Watts GF, Mori TA, Barrett PH, Beilin LJ, Redgrave TG. Factorial study of the effects of atorvastatin and fish oil on dyslipidaemia in visceral obesity. Eur J Clin Invest 2002;32:429–436. [PubMed: 12059988]
36. Davidson MH, Stein EA, Bays HE, Maki KC, Doyle RT, Shalwitz RA, Ballantyne CM, Ginsberg HN. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther 2007;29:1354–1367. [PubMed: 17825687]
37. Liu J, Sempos CT, Donahue RP, Dorn J, Trevisan M, Grundy SM. Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. Am J Cardiol 2006;98:1363–1368. [PubMed: 17134630]

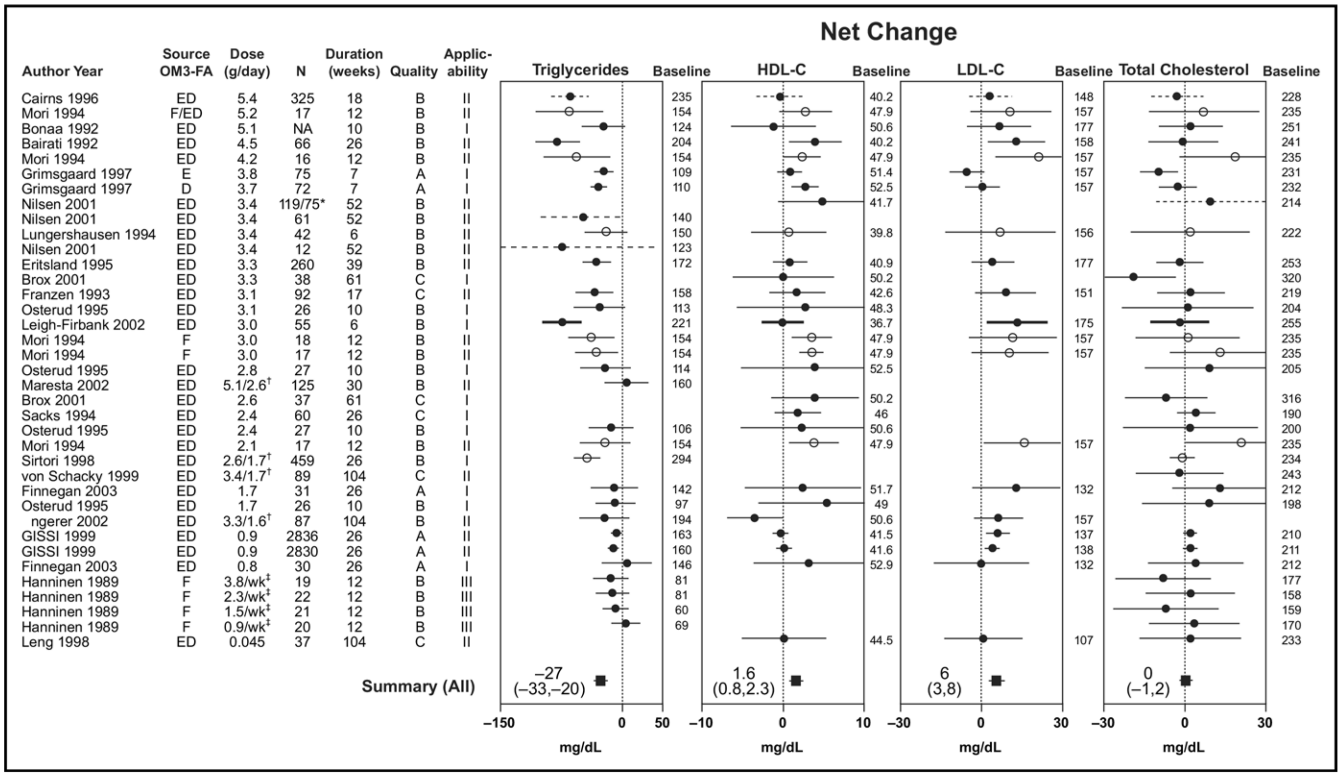

Figure 1.

Meta-analysis of randomized controlled trials of the effect of OM3-FAs on lipid values. Studies are arranged by OM3-FA dose (grams per day). The point estimates of the net changes (change in OM3-FA arm minus change in control arm) and the corresponding 95% confidence intervals for individual studies are indicated by *circles* and *bars*. The random-effects model summary results are indicated by *squares* and *bars* near the bottom. *Black circles* indicate that data came from text or tables; *open circles* indicate that data were estimated from graphs; *thick solid 95% confidence interval* indicates that the SE of the net change was reported; *thin solid 95% confidence interval* indicates that the SE of net change was estimated from either baseline and final SEs or SEs of cohort changes; *dashed 95% confidence interval* indicates that the SE of net change was estimated from other sources. Quality: A = Least bias; study mostly adheres to the commonly held concepts of good quality, including formal randomized study, clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; <20% dropout; clear reporting of dropouts; and no obvious bias. B = Susceptible to some bias; study has some deficiencies but none likely to cause major bias or may be missing information making assessment of the limitations and potential problems difficult. C = Significant bias; study has serious errors in design, analysis, or reporting or may have large amount of missing information or discrepancies in reporting. Applicability: I = Sample is representative of the population of interest; sufficiently large to cover both genders, a wide age range, and other important features of the target population, including baseline dietary intake broadly similar to that of the United States population. II = Sample is representative of a relevant subgroup of the target population, but not the entire population. III = Sample is representative of a narrow subgroup of subjects only and not well applicable to other subgroups. *N = 119 for HDL cholesterol (HDL-C) and n = 75 for total cholesterol. †Initial dose given for 2 to 3 months, followed by lower dose for remainder of study. D = docosahexaenoic acid; E =

eicosapentaenoic acid; ED = E + D; F = fish oil; LDL-C = LDL cholesterol. Reprinted with permission from *Atherosclerosis*.[27]

Table 1

Lipid and lipoprotein results

Variable	Simvastatin Plus Placebo (n = 132)						Simvastatin Plus P-OM3 (n = 122)						p Value (Between-Group % Change)
	Baseline		End of Treatment		% Change		Baseline		End of Treatment		% Change		
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	
Non-HDL cholesterol (mg/dl)	141 ± 29	141	139 ± 32	134	−1.5 ± 11	−2.2	136 ± 25	137	124 ± 25	123	−7.9 ± 14	−9.0	<0.0001
TG (mg/dl)	287 ± 78	271	276 ± 99	260	−3.5 ± 22	−6.3	282 ± 76	268	202 ± 77	182	−28 ± 19	−30	<0.0001
VLDL cholesterol (mg/dl)	53 ± 10	52	50 ± 12	49	−4.8 ± 17	−7.2	52 ± 11	52	40 ± 13	37	−24 ± 27	−28	<0.0001
LDL cholesterol (mg/dl)	92 ± 23	88	90 ± 24	85	−1.9 ± 12	−2.8	89 ± 22	91	90 ± 20	88	3.4 ± 19	0.7	0.0522
HDL cholesterol (mg/dl)	45 ± 9.3	43	44 ± 8.8	44	−1.1 ± 9.0	−1.2	47 ± 12	46	49 ± 13	48	4.1 ± 9.3	3.4	<0.0001
TC (mg/dl)	186 ± 32	184	183 ± 35	178	−1.5 ± 9.2	−1.7	183 ± 28	184	173 ± 25	172	−4.7 ± 11	−4.8	0.0013
TC/HDL cholesterol ratio	4.3 ± 0.8	4.2	4.3 ± 0.9	4.1	0.1 ± 9.6	−0.7	4.0 ± 0.9	3.9	3.7 ± 1.0	3.5	−8.0 ± 11	−9.6	<0.0001
Apolipoprotein B (mg/dl)	87 ± 15	87	86 ± 17	85	−1.2 ± 11	−1.9	85 ± 15	86	81 ± 15	80	−3.8 ± 13	−4.2	0.0232

To convert non-HDL cholesterol, VLDL cholesterol, LDL cholesterol, HDL cholesterol, and TC to millimoles per liter, multiply by 0.0259. To convert TG to millimoles per liter, multiply by 0.0113. To convert apolipoprotein B to grams per liter, multiply by 0.01. All data points ≥10 are rounded to the nearest ones digit. p >0.05 for between-group comparisons in all baseline values, except for TC/HDL cholesterol ratio (p = 0.012).

TC = total cholesterol; TG = triglyceride.