Switching from EPA + DHA (Omega-3-acid Ethyl Esters) to High-Purity EPA (Icosapent Ethyl) in a Statin-Treated Patient with Persistent Dyslipidemia and High Cardiovascular Risk: A Case Study

James R. Crandell
Private Practice, Lakewood, OH, USA.

ABSTRACT: Cardiovascular (CV) risk may remain despite statin treatment, and there is a need to address this risk with add-on therapy. The lipid effects of two different prescription omega-3 fatty acid therapies are described in a 55-year-old statin- and niacin-treated female with severe dyslipidemia and high CV risk. The patient was initially treated with omega-3-acid ethyl esters (icosapentenoic acid [EPA] and docosahexaenoic acid) 4 g/day. Due to persistently elevated low-density lipoprotein cholesterol (LDL-C), she was switched to icosapent ethyl (high-purity EPA ethyl ester) 4 g/day. Approximately 28 months after switching to icosapent ethyl, her LDL-C decreased by 69% to 52 mg/dL, triglycerides decreased by 35% to 119 mg/dL, non-high-density lipoprotein cholesterol (non-HDL-C) decreased by 63% to 76 mg/dL, total cholesterol decreased by 44% to 137 mg/dL, and HDL-C increased by 45% to 61 mg/dL. Total and small dense LDL particle concentrations decreased by 60 and 59%, respectively. Treatment was well tolerated, with improvements maintained over two years.

KEYWORDS: docosahexaenoic acid, eicosapentenoic acid, hypertriglyceridemia, icosapent ethyl, Lovaza, Vascepa

Introduction
Addressing residual cardiovascular (CV) risk in patients on optimized statin treatment is an unmet need in CV disease management.1 Prescription omega-3 fatty acids are effective treatments for hypertriglyceridemia and may have an important role in reducing residual CV risk, given that elevated triglyceride (TG) levels have been implicated in the causal pathway of CV disease.2–9

In addition to TG-lowering effects, the omega-3 fatty acids eicosapentenoic acid (EPA) and docosahexaenoic acid (DHA) have demonstrated benefits on other potential atherogenic parameters that have been identified as potential contributors to residual CV risk, including apolipoprotein B (Apo-B), non-high-density lipoprotein cholesterol (non-HDL-C), and lipoprotein particles.7–13 Other beneficial CV effects on heart rate, arrhythmia, blood pressure, systemic vascular resistance, myocardial efficiency, arterial wall compliance, vasodilatory responses, and thrombosis have also been noted.14 EPA has been shown to have antioxidant properties and to be incorporated into membrane phospholipids, including the atherosclerotic plaque itself where it exerts beneficial and pleiotropic effects on endothelial function, macrophage function, monocyte function, foam cell formation, inflammation, plaque progression, plaque formation, plaque vulnerability, and thrombus formation, all of which are involved in the development and progression of atherothrombotic processes.15

Omega-3-acid ethyl esters (Lovaza®, GlaxoSmithKline) is a prescription product containing the ethyl esters of EPA and DHA.16 Icosapent ethyl (Vascepa®; Amarin Pharma Inc.) is a high-purity prescription formulation of the ethyl ester of EPA; both are currently indicated as an adjunct to diet to reduce TG levels in adult patients with severe hypertriglyceridemia (≥500 mg/dL).16,17 In randomized, placebo-controlled clinical studies of patients with very high TG levels (500–2000 mg/dL; with or without statins) and in studies of patients with high TG levels (200–499 mg/dL; all statin treated), prescription omega-3 fatty acids have consistently demonstrated significant and substantial reductions in TG levels.7–8,18–21 However, in these studies, differential effects on low-density
lipoprotein cholesterol (LDL-C) have been observed between products containing combinations of DHA and EPA when compared with products containing high-purity EPA. Cumulative clinical evidence from these studies, as well as from systematic reviews and meta-analyses that included studies of EPA and DHA alone, has shown that DHA may increase LDL-C levels, whereas EPA has a neutral effect.7-9,19-23

This report describes a high-risk, statin-treated patient and the impact of switching from prescription omega-3-acid ethyl esters (ethyl esters of EPA and DHA) to prescription icosapent ethyl (high-purity EPA ethyl ester) on her lipid or lipoprotein profile over a follow-up period of more than two years.

**Case**

**Patient history.** A 55-year-old, overweight, female patient with a history of severe dyslipidemia and insulin resistance has been followed up for >14 years in a private cardiology practice. She has a complicated medical history, including severe depression, vasodepressor-type orthostatic hypotension, near syncope, and long-standing multiple sclerosis, which has been stable in recent years but was previously treated with intermittent steroids via a mediport. She was previously treated with balloon angioplasty for superior vena cava occlusion at the steroid mediport site. Her recent history (past year) was also notable for stage 1 breast cancer, which was treated with bilateral mastectomy (no metastases) but without aggressive chemotherapy that would be expected to interfere with her lipid or lipoprotein profile. The patient is a smoker with a strong family history of CV disease in her first-degree relatives (mother has dyslipidemia and non-ischemic cardiomyopathy with multifocal atrial tachycardia; father had non-ST-segment elevation myocardial infarction and early-onset multivessel carotid disease requiring carotid endarterectomy and bypass). The patient's non-lipid-lowering medications included oscarbazine, sertraline, lamotrigine, alprazolam, oxbytunin, ramitidine, albulter, aspirin, metoprolol, midodrine, naproxen, baclofen, and tizanidine. During the course of care described herein, the parameters of lifestyle, including diet and exercise, remained stable per patient self-reporting; there was less than 14 lbs of weight change and no changes in fasting blood sugar control. There was no history of chronic heart failure, percutaneous coronary intervention, or catherization, and the patient's pharmacologic nuclear stress test results were negative; no invasive cardiac studies were performed.

**Lipid-lowering medications.** Prior to the initiation of any omega-3 fatty acid treatments, the patient's lipid-lowering medications included rosuvastatin 40 mg/day and extended-release niacin 1500 mg/day. Niacin had been introduced in an attempt to improve LDL-C levels given the patient's poor response to aggressive statin therapy. Despite stable doses of her statin and niacin regimens, the patient continued to have elevations in atherogenic lipid parameters, including LDL-C 161 mg/dL, TGs 240 mg/dL, non-HDL-C 209 mg/dL, and total cholesterol (TC) 252 mg/dL. In addition, her HDL-C level was 43 mg/dL. Based on these findings, omega-3-acid ethyl esters 4 g/day (given as 2 g twice daily) was added to her existing lipid-lowering regimen; at the time, omega-3-acid ethyl esters was the only US Food and Drug Administration (FDA)-approved prescription omega-3 fatty acid product available.

After 10 months on stable doses of omega-3-acid ethyl esters in combination with stable doses of rosuvastatin and extended-release niacin along with weight loss of approximately 13 lbs in the previous six to nine months, the patient's lipid profile revealed reduction in TG levels to 182 mg/dL (Table 1 and Fig. 1). (All lipid profiles were measured by nuclear magnetic resonance [NMR] spectroscopy by Cleveland Clinic Laboratories.) There were minimal to no improvements in non-HDL-C, TC, and HDL-C levels. Most concerning was the persistently elevated LDL-C level of 168 mg/dL. In addition, her NMR lipoprotein profile revealed elevated lipoprotein particle concentrations with an LDL particle (LDL-P) concentration of 1772 nmol/L and a small dense LDL-P concentration of 715 nmol/L. Based on these results, the patient's strong family history of CV disease, and data regarding the differential effects of EPA and DHA on LDL-C, omega-3-acid ethyl esters treatment was switched to the prescription EPA-only omega-3 fatty acid, icosapent ethyl.

**Impact of switching to icosapent ethyl on lipid profile.** After approximately one year of treatment with icosapent ethyl 4 g/day as add-on therapy to her original lipid-lowering regimen (stable rosuvastatin and extended-release niacin) and without any significant changes in weight to date, the patient's NMR lipid and lipoprotein profile showed substantial improvement compared with her lipid profile while on omega-3-acid ethyl esters treatment (Table 1 and Fig. 1): LDL-C level decreased by 52% to 80 mg/dL, TG level decreased by 29% to 130 mg/dL, non-HDL-C level decreased by 48% to 106 mg/dL, TC level decreased by 37% to 156 mg/dL, and HDL-C level increased by 19% to 50 mg/dL. In addition, her total LDL-P concentration decreased by 27% to 1297 nmol/L and her small dense LDL-P concentration decreased by 87% to 91 nmol/L.

The most recent follow-up NMR lipid profile for this patient demonstrated ongoing improvements in lipid parameter levels over 28 months with stable weight and continued icosapent ethyl add-on treatment (Table 1 and Fig. 1): LDL-C, 52 mg/dL; TG, 119 mg/dL; non-HDL-C, 76 mg/dL; and TC, 137 mg/dL. Her LDL-P concentration was 706 nmol/L, and her small dense LDL-P concentration was 296 nmol/L; both values were approximately 60% lower than levels reported prior to the switch from omega-3-acid ethyl esters to icosapent ethyl. Although Apo-B measurements for this patient were not available prior to initiation of icosapent ethyl, measurements after the switch show a reduction from 99 mg/dL at
# Treatment of persistent dyslipidemia with high cardiovascular risk

This case illustrates that switching from omega-3-acid ethyl esters to icosapent ethyl improved a broad range of potentially atherogenic parameters in a patient with high residual CV risk, despite treatment with a statin and niacin. Both prescription omega-3 fatty acid products were well tolerated, with no observed or reported issues concerning adverse effects, drug interactions, or adherence to treatment in this patient.

## Table 1. Lipid and lipoprotein parameters before and after switching from omega-3-acid ethyl esters (EPA + DHA) to icosapent ethyl (high-purity EPA) in a statin-treated patient.

| Lipid and lipoprotein parameters | ON OMEGA-3-ACID ETHYL ESTERS | ON ICOSAPENT ETHYL | ON ICOSAPENT ETHYL |
|----------------------------------|------------------------------|--------------------|--------------------|
|                                  | 4 g/day (10 MONTHS)         | 4 g/day (=1 YEAR)* | 4 g/day (=2 YEARS)* |
| **LDL-C, mg/dL**                 | 168†                         | 80‡                 | 52§                 |
| % change                         | −52.4                        | −69.1               |
| **TGs, mg/dL**                   | 182                          | 130                | 119                |
| % change                         | −28.6                        | −34.6               |
| **Non-HDL-C, mg/dL**             | 204                          | 106                | 76                 |
| % change                         | −48.0                        | −62.8               |
| **TC, mg/dL**                    | 246                          | 156                | 137                |
| % change                         | −36.6                        | −44.3               |
| **VLDL-C, mg/dL**                | 32                           | 25                 | 22                 |
| % change                         | −21.9                        | −31.3               |
| **HDL-C, mg/dL**                 | 42                           | 50                 | 61                 |
| % change                         | +19.1                        | +45.2               |
| **Apo-B, mg/dL**                 | Not available                | 99                 | 64                 |
| % change                         | Not calculated               | Not calculated     |

### Lipoprotein particle concentration

| Lipoprotein particle concentration | ON OMEGA-3-ACID ETHYL ESTERS | ON ICOSAPENT ETHYL |
|-----------------------------------|------------------------------|--------------------|
| Large VLDL-P, nmol/L              | 5.6                          | <0.7               |
| % change                          | Not calculated (value too low) | Not calculated (value too low) |
| **LDL-P, nmol/L**                 | 1772                         | 1297               | 706                |
| % change                          | −26.8                        | −60.2               |
| sdLDL-P, nmol/L                   | 715                          | 91.0               | 296.0              |
| % change                          | −87.3                        | −58.6               |
| Large HDL-P, µmol/L               | 1.7                          | 4.7                | 10.0               |
| % change                          | +176.5                       | +488.2             |
| HDL-P, µmol/L                     | 28.1                         | 28.4               | 32.5               |
| % change                          | +1.1                         | +15.7              |

### Lipoprotein particle size

| Lipoprotein particle size | ON OMEGA-3-ACID ETHYL ESTERS | ON ICOSAPENT ETHYL |
|--------------------------|------------------------------|--------------------|
| VLDL-P, nm               | 45.8                         | Too low to determine | 43.4   |
| % change                 | Not calculated               | −5.2               |
| LDL-P, nm                | 21.4                         | 21.1               | 20.7               |
| % change                 | −1.4                         | −3.3               |
| HDL-P, nm                | 8.4                          | 9.8                | 10.0               |
| % change                 | +16.7                        | +19.1              |

Notes: *Patient was on stable doses of rosuvastatin and extended-release niacin. †Percent changes shown are for icosapent ethyl compared with omega-3-acid ethyl esters treatment. ‡LDL-C level was calculated via the Friedewald equation: LDL-C = TC − HDL-C − (TG/5). §LDL-C level was measured directly. ‡Non-HDL-C values calculated as TC − HDL-C. ‡VLDL-C values from standard lipid panel (not reported in NMR).

Abbreviations: Apo-B, apolipoprotein B; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; HDL-P, high-density lipoprotein particle; LDL-C, low-density lipoprotein cholesterol; LDL-P, low-density lipoprotein particle; non-HDL-C, non-high-density lipoprotein cholesterol; sdLDL-P, small dense low-density lipoprotein particle; TC, total cholesterol; TGs, triglycerides; VLDL-C, very-low-density lipoprotein cholesterol; VLDL-P, very-low-density lipoprotein particle.

Approximately one year of treatment to 64 mg/dL at the most recent follow-up.
This report describes a patient with severe dyslipidemia and high residual CV risk, despite stable lipid-lowering treatment with a statin and extended-release niacin in a private cardiology practice. Addition of prescription omega-3-acid ethyl esters 4 g/day (EPA + DHA) to her lipid-lowering regimen improved TG levels, but her LDL-C level was 168 mg/dL, a cause for concern given her high CV risk and strong family history of CV disease. Based on her persistently elevated LDL-C level, as well as evidence that the EPA-only omega-3 fatty acid product icosapent ethyl had not increased LDL-C levels compared with placebo,\textsuperscript{8,17,20} the patient was switched from omega-3-acid ethyl esters to icosapent ethyl 4 g/day. After approximately one year of treatment with icosapent ethyl, she experienced substantial reductions in levels of LDL-C, TG, non-HDL-C, and TC and improvements in LDL-P and small dense LDL-P concentrations. Most of these parameters continued to improve during an additional 16 months of ongoing icosapent ethyl treatment.

The lipid profile changes demonstrated in the current case study are consistent with other reports of patients being switched from EPA + DHA products to icosapent ethyl.\textsuperscript{24–27} A retrospective chart review of 10 patients (9 treated with statins) with prediabetes or diabetes showed that switching from omega-3-acid ethyl esters 4 g/day to icosapent ethyl 4 g/day was well tolerated and resulted in improvements in the levels of LDL-C, TG, non-HDL-C, TC, and HDL-C for most patients.\textsuperscript{24} Similarly, another retrospective case series of 15 patients (10 treated with statins) with elevated TG levels or hyperlipidemia showed that the switch from omega-3-acid

**Figure 1.** Changes in lipid parameters (A) and lipoprotein parameters (B) at approximately one year and more than two years after switching from omega-3-acid ethyl esters (EPA + DHA) to icosapent ethyl (high-purity EPA). Patient was on stable doses of rosuvastatin and extended-release niacin. Percent changes shown are for icosapent ethyl compared with omega-3-acid ethyl esters treatment.

**Abbreviations:** DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LDL-P, low-density lipoprotein particle concentration; non-HDL-C, non-high-density lipoprotein cholesterol; sdLDL-P, small dense low-density lipoprotein particle concentration; TC, total cholesterol; TGs, triglycerides; VLDL-C, very-low-density lipoprotein cholesterol.

**Discussion**

This report describes a patient with severe dyslipidemia and high residual CV risk, despite stable lipid-lowering treatment with a statin and extended-release niacin in a private cardiology practice. Addition of prescription omega-3-acid ethyl esters 4 g/day (EPA + DHA) to her lipid-lowering regimen improved TG levels, but her LDL-C level was 168 mg/dL, a cause for concern given her high CV risk and strong family history of CV disease. Based on her persistently elevated LDL-C level, as well as evidence that the EPA-only omega-3 fatty acid product icosapent ethyl had not increased LDL-C levels compared with placebo,\textsuperscript{8,17,20} the patient was switched from omega-3-acid ethyl esters to icosapent ethyl 4 g/day. After approximately one year of treatment with icosapent ethyl, she experienced substantial reductions in levels of LDL-C, TG, non-HDL-C, and TC and improvements in LDL-P and small dense LDL-P concentrations. Most of these parameters continued to improve during an additional 16 months of ongoing icosapent ethyl treatment.

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ethyl esters 4 g/day to icosapent ethyl 4 g/day was associated with reductions in LDL-C, TG, non-HDL-C, and TC levels (changes in HDL-C levels were variable). These findings are notable in that such patients, due to their atherogenic lipid profiles and/or other relevant conditions, may be at residual CV risk despite statin therapy.

The primary reason for the treatment switch from omega-3-acid ethyl esters to icosapent ethyl was to potentially address the patient’s persistently elevated LDL-C level. Significant LDL-C level increases were observed in phase 3 clinical trials of omega-3-acid ethyl esters in patients with very high TG levels (≥500 mg/dL), and thus all EPA + DHA combination omega-3 fatty acid products include language in their prescribing information warnings and precautions that LDL-C levels may rise during treatment and should be monitored. In contrast, icosapent ethyl did not increase LDL-C levels compared with placebo in phase 3 clinical trials, and the prescribing information does not include warnings and/or precautions pertaining to LDL-C.

The LDL-P and small dense LDL-P response associated with switching from omega-3-acid ethyl esters to icosapent ethyl in this patient is noteworthy. After approximately one year on icosapent ethyl, reductions of 27% and 87% were observed in LDL-P and small dense LDL-P concentrations, respectively. Substantial reductions in both LDL-P and small dense LDL-P concentrations were still evident at the most recent follow-up (more than two years). While the clinical implications of these findings are not well established, LDL-P is an emerging marker for CV risk and may influence atherogenicity. Parameters such as LDL-P can help provide a more complete assessment of CV risk than LDL-C alone and thus help guide clinical decisions regarding treatment for dyslipidemia.

Increased LDL-P is associated with greater diffusion of LDL particles into the arterial wall, where LDL particles may undergo oxidative modification and uptake by tissue macrophages, forming foam cells and thus promoting atherosclerosis. Elevated LDL-P, particularly in patients on lipid-lowering medications, may be more predictive of residual CV risk than LDL-C and non-HDL-C. The 2015 National Lipid Association Expert Panel on Patient-Centered Management of Dyslipidemia has suggested that LDL-P may have clinical utility, especially in patients who have achieved non-HDL-C and LDL-C goals. Both large and small LDL particles have been reported to have an association with CV mortality. Small dense LDL particles are among the best characterized and may be associated with greater atherogenicity than larger particles (due to relative ease of oxidation) and increased risk for CV disease.

The icosapent ethyl-associated improvements in lipoprotein particles reported in this statin-treated patient are generally consistent with subanalyses from phase 3 randomized clinical studies of icosapent ethyl in patients with very high or high TG levels. Beneficial effects of icosapent ethyl on LDL-P were first reported in a prespecified exploratory analysis of patients with very high TG levels (≥500 and ≤2000 mg/dL) who participated in the Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-week study with an open-label Extension (MARINE). Among patients with NMR lipoprotein particle data assessments, 12 weeks of treatment with icosapent ethyl 4 g/day produced significant reductions in large very-low-density lipoprotein particle (VLDL-P), total LDL-P, small dense LDL-P, and total HDL-P concentrations and a significant reduction in VLDL-P size compared with placebo. More recently, a prespecified exploratory analysis of the ANCHOR study reported lipoprotein profile findings in patients with TG levels ≥200 to <500 mg/dL and LDL-C ≥40 to ≤100 mg/dL, despite statin treatment. Among patients with NMR lipoprotein particle assessments, 12 weeks of treatment with icosapent ethyl 4 g/day produced significant reductions in concentrations of total VLDL-P, large VLDL-P, total LDL-P, small dense LDL-P, total HDL-P, and large HDL-P compared with placebo. In addition, icosapent ethyl 4 g/day significantly reduced VLDL-P and HDL-P size while slightly increasing LDL-P size compared with placebo.

The impact of icosapent ethyl on lipid and lipoprotein parameters and the implications for CV outcomes are being investigated in the Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT; ClinicalTrials.gov identifier: NCT01492361), a randomized, placebo-controlled, clinical study currently underway and evaluating icosapent ethyl 4 g/day in combination with statins in patients with hypertriglyceridemia and high CV risk. The results of the recent Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) have underscored the principle behind statin add-on therapy as a strategy to reduce residual CV risk and the importance of ensuring low LDL-C levels.

Although this current report is limited to a single retrospective case and results may not necessarily be extrapolated to patients with different demographic and clinical characteristics, the collective evidence from this and other retrospective case reports/series published to date suggests that improvements in lipid parameters may be achieved after switching from products containing both DHA and EPA to the prescription EPA-only product, icosapent ethyl. Taken together, these case studies suggest that a prospective clinical study examining the impact of such a switch with a much larger sample size may be warranted. In addition, FDA equivalence code indicates that products containing DHA are not therapeutically equivalent to icosapent ethyl, and therefore, such products should not be substituted for icosapent ethyl. Other limitations of this report include the patient’s history of breast cancer, which may have affected her lipid and lipoprotein results, although no obvious chemotherapy-specific pharmacologic etiology was noted. In this real-world setting, another limitation was that parameters such as fasting prior to lipid and lipoprotein measurements, medication adherence, and diet and exercise stability were reported by the patient and were thus not verifiable. Finally, the report focuses only
on lipid and lipoprotein results and not CV outcomes. Icosa-
pent ethyl is not approved by the US FDA to reduce the risk of coronary heart disease. The effect of icosapent ethyl on the risk of CV mortality and morbidity has not been determined. The benefits of icosapent ethyl on CV outcomes remain to be proven and are currently being investigated in REDUCE-IT.

Conclusions
In this statin-treated patient with high residual CV risk and strong familial risk factors for CV disease, switching from omega-3-acid ethyl esters (prescription EPA + DHA) to ico-
sapent ethyl (prescription high-purity EPA) was well tolerated and substantially improved lipid or lipoprotein parameters, including LDL-C, non-HDL-C, VLDL-C, LDL-P, and small dense LDL-P. In general, improvements in lipid and lipoprotein parameters were maintained with icosapent ethyl treatment over two years.

Author Contributions
JRC conducted the case study, analyzed the data, contributed to the writing of the manuscript, agrees with manuscript results and conclusions, developed the structure and arguments for the paper, made critical revisions, and approved the final version for submission. The author reviewed and approved of the final manuscript.

REFERENCES
1. Frochart JC, Davignon J, Hermans MP, et al. Residual macrovascular risk in 2013: what have we learned? Cardiovasc Diabetol. 2014;13(1):26.
2. Ginsberg HN. Hypertriglyceridemia: new insights and new approaches to phar-
macologic therapy. Am J Cardiol. 2001;87(10):1174–80.
3. Jorgensen AB, Frikke-Schmidt R, Nordergaard BG, Thybjerg-Hansen A. Loss-
of-function mutations in APOC3 and risk of ischemic vascular disease. N Engl J Med. 2014;371(1):32–41.
4. Crosby J, Peloso GM, Auer PL, et al, for the TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. N Engl J Med. 2014;371(1):22–31.
5. A Study of AMR101 to Evaluate Its Ability to Reduce Cardiovascular Events in High Risk Patients with Hypertriglyceridemia and on Statin (REDUCE-IT). Available at: https://clinicaltrials.gov/show/NCT01492361. Accessed March 28, 2016.
6. Outcomes Study to Assess STrain Residual Risk Reduction With EpaNovo in HiGH CV Risk Patients (STRIMENTH). Available at: http://clinicaltrials.gov/ct2/show/NCT02148171?term = strengthstrain&ovmaga=
7. Maki KC, Osdoff DG, Nichols SJ, et al. A highly bioavailable omega-3 free fatty acid formulation improves the cardiovascular risk profile in high-risk, statin-
treated patients with residual hypertriglyceridemia (the ESPRIT trial). Clin Ther. 2013;35(9):1400–11.
8. Ballantyne CM, Bays HE, Kastelein JJ, et al. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). Am J Cardiol. 2012;110(7):984–92.
9. Davidson MH, Stein EA, Bays HE, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceri-
demic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther. 2007;29(7):1354–67.
10. Jacobson TA, Ino MK, Maki KC, et al. National Lipid Association recommenda-
tions for patient-centered management of dyslipidemia: part 1 – executive sum-
mary. J Clin Lipidol. 2014;8:473–88.
11. Q Johnston I, Buysschaert M, Hermans MP. Hypertriglyceridemia and residual dyslipidemia in statin-treated, patients with diabetes at the highest risk for car-
diovascular disease and achieving very-low-density lipoprotein-cholesterol levels. J Clin Lipidol. 2012;6(5):434–42.
12. Bays HE, Breckman RA, Ballantyne CM, et al. Icosapent ethyl, a pure EPA omega-3 fatty acid: effects on lipoprotein particle concentration and size in patients with very high triglyceride levels (the MARINE study). J Clin Lipidol. 2012;6(6):565–72.
13. Ballantyne CM, Breckman RA, Bays HE, et al. Effects of icosapent ethyl on lipoprotein particle concentration and size in statin-treated patients with persis-
tent high triglycerides (the ANCHOR Study). J Clin Lipidol. 2015;9(3):377–83.
14. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol.
2011;58(20):2047–67.
15. Borow KM, Nelson JR, Mason RP. Biologic plausibility, cellular effects, and molecular mechanisms of eicosapentaenoic acid (EPA) in atherosclerosis. Atherosclerosis. 2015;242(1):357–66.
16. Davidson MH, Stein EA, Bays HE, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceri-
demic patients: an 8-week, randomized, double-blind, placebo-controlled study with an open-label Extension [MARINE] trial. Am J Cardiol. 2011;108(5):682–90.
17. Kastelein JJP, Maki KC, Susekov A, et al. Omega-3 free fatty acids for the treat-
ment of severe hypertriglyceridemia: the EpanoVa Or Lowering Very high trig-
lycEridEs (EVOLVE) trial. J Clin Lipidol. 2014;8(3):94–108.
18. Wu MY, Jacobson TA. Effects of eicosapentaenoic acid versus docosahexaenoic acid on serum lipids: a systematic review and meta-analysis. Curr Atheroscler Rep. 2011;13(6):474–83.
19. Jacobson TA, Glickstein SB, Rowe JD, Soni PN. Effects of eicosapentaenoic acid and docosahexaenoic acid on low-density lipoprotein cholesterol and other lipids: a review. J Clin Lipidol. 2012;6(1):5–18.
20. Hassan A, Tadjoudin N, Shaikh A. Retrospective case series of patients with dia-
etes or prediabetes who were switched from omega-3-acid ethyl esters to icosap-
ten ethyl. Cardiol Thor. 2015;4(1):83–93.
21. Hillman DE, Malekzer MA. Potential benefits of icosapent ethyl on the lipid profile: case studies. Clin Med Insights Cardiol. 2014;8:13–5.
22. Castaldo RS. A retrospective case series of the lipid effects of switching from omega-3 fatty acid ethyl esters to icosapent ethyl in hyperlipidemic patients. Postgrad Med. 2014;129(3):268–73.
23. Crandell J, Tartaglia C, Tartaglia J. Retrospective case series of lipid effects in patients switched from EPA + DHA (omega-3 acid ethyl ester) to high-purity EPA (icosapent ethyl) [abstract 124]. Clin Lipidol. 2015;38(suppl 1):12.
24. Omtryg [package insert]. Arlington, VA: Trygg Pharma, Inc; 2014.
25. Epanova [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2016.
26. Sniderman AD, Kiviterovich PO. Update on the detection and treatment of ath-
erogenic low-density lipoproteins. Curr Opin Endocrinol Diabetes Obes. 2013;20(2):140–7.
27. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular dis-
ease: a scientific statement from the American Heart Association. Circulation. 2011;123(20):2292–333.
28. Superko HR, Gadesam RR. Is it LDL particle size or number that correlates with risk for cardiovascular disease? Curr Atheroscler Rep. 2008;10(5):377–85.
29. Bays HE, Jones PH, Brown WV, Jacobson TA; National Lipid Association. National lipoprotein association annual summary of clinical lipidolgy. J Clin Lipidol. 2014;8(6 Suppl):S1–36.
30. Grammer TB, Kleber ME, Marz W, et al. Low-density lipoprotein particle diameter and mortality: the Ludwigshafen Risk and Cardiovascular Health Study. Eur Heart J. 2015;36(31):331–8.
31. Tribble DL, Rizzo M, Chait A, Lewis DM, Blanche PJ, Krauss RM. Enhanced oxidative susceptibility and reduced antioxidant content of metabolic precursors of small, dense low-density lipoproteins. Am J Med. 2001;110(2):103–10.
32. Stampfer MJ, Krauss RM, Ma J, et al. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. JAMA. 1996;276(11):882–8.
33. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin ther-
apy after acute coronary syndromes. N Engl J Med. 2015;372(25):2387–97.
34. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. U.S. Food and Drug Administration. Available at: http://www.accessdata.
dfa.gov/scripts/cdrhob/. Accessed March 28, 2016.
35. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18(6):499–502.