



A NEW APPROACH TO REDUCING CARDIOVASCULAR RISK - BEYOND LDL

Recent data from the Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial (REDUCE-IT) suggest that the use of a highly purified prescription [omega-3] fatty acid product (icosapent ethyl [IPE]) can significantly lower the risk of cardiovascular disease (CVD) in patients with triglyceride TG levels of 135 to 499 mg/dL while treated with statin therapy.¹ These findings support a change in practice for preventing CVD. Based on these findings, IPE is indicated as an adjunct to maximally tolerated statin therapy to reduce the risk of CVD events in adult patients with elevated triglyceride levels (≥ 150 mg/dL) and established CVD or diabetes and 2 or more additional risk factors for CVD.

THE LINK BETWEEN TRIGLYCERIDES AND CARDIOVASCULAR DISEASE

CVD is the leading cause of death in the United States.¹ High levels of low-density lipoprotein cholesterol (LDL-C) are strongly associated with the risk for CVD.² Treatment with a statin to lower LDL-C levels is a key recommendation for preventing CVD in high-risk patients. However, despite CVD risk reductions with statin therapy, many patients using statins remain at substantial risk for future cardiovascular events.

Elevated TGs have been identified as a factor that can predict the risk for CVD in statin-treated patients.^{3,4} Elevated TGs can occur in patients receiving optimal statin treatment and those with well-controlled LDL-C (e.g., <70 mg/dL).⁵

The association between elevated TGs and CVD risk has been demonstrated in epidemiologic studies. For example, the Framingham Heart Study and the Prospective Cardiovascular Münster (PROCAM) study have found that the lowest TG levels (<100 mg/dL) correlate with the lowest CVD risk.^{6,7} TGs above 150 mg/dL have been shown to be associated with increased CVD risk.^{8,9} Risk for CVD rises as TGs rise and peaks at TG levels of approximately 600–800 mg/dL. CVD risk decreases somewhat at TG concentrations above this level, but remains elevated. As TGs exceed 1,000 mg/dL, the risk of pancreatitis increases. In a 22-year follow-up of the Bezafibrate Infarction Prevention study and registry, all-cause mortality was increased by 68% in patients with TGs ≥ 500 mg/dL compared with those whose TGs were <100 mg/dL.¹⁰

According to the American Heart Association (AHA) Scientific Statement on TGs and CVD, TG levels are classified as follows:¹¹

- Optimal: <100 mg/dL
- Normal: <150 mg/dL
- Borderline high: 150–199 mg/dL
- High: 200–499 mg/dL
- Very high: ≥ 500 mg/dL

It is important to note that TG levels ≥ 175 mg/dL are listed as a risk modifier in the 2018 AHA/American College of Cardiology cholesterol guideline and can be used to support use of statin therapy in primary prevention patients.¹² Clinicians are advised to address and treat lifestyle factors (e.g., obesity, metabolic syndrome), secondary factors (e.g., diabetes mellitus, chronic liver or kidney disease, hypothyroidism), and medications that increase TG levels in those with moderate hypertriglyceridemia (TG levels 175–499 mg/dL).¹²

Elevated TGs are common in the United States—nearly one in four adults has a TG level classified as borderline high or higher.¹³ TGs contribute to CVD risk through multiple indirect mechanisms. They are associated with activation of proinflammatory signaling pathways that promote endothelial dysfunction and accelerate plaque formation associated with atherosclerosis.¹⁴ Additionally, they enhance thrombogenicity and clot formation.¹⁵





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Traditional Approaches to Reducing CVD Risk

- Lifestyle approaches (e.g., regular exercise, heart healthy diet such as the Mediterranean or Dietary Approaches to Stop Hypertension [DASH] type diet) along with statin therapy are recommended as first-line treatment for patients with elevated LDL-C and other CVD risk factors and have been clearly demonstrated to reduce the risk of CVD and all-cause mortality.
- Statins primarily lower total cholesterol and LDL-C, but they also lower TGs and are used as first-line pharmacological treatment for most patients with borderline high, high, and very high TGs.
- Additional medications may be used, depending on patient characteristics.

Impact of Treatment to Lower TGs on Patient Outcomes—Historical Perspective

Until recently, there was little evidence that treatment with non-statin medications that reduce TGs, including niacin and fibrates, improved CVD outcomes for patients, compared with statin treatment and other contemporary medical therapy. See Table 1 for historical perspective. More recent data suggest that treatment with omega-3 fatty acids can provide added benefits to statins for reducing cardiovascular outcomes.

Omega-3 Fatty Acid Products

Currently, two prescription omega-3 fatty acids are available in the U.S. for the treatment of hypertriglyceridemia (≥ 500 mg/dL) as an adjunct to diet

(Table 2). As prescription products, they undergo the same strict U.S. Food and Drug Administration (FDA) regulation processes as other prescription medications.

Table 2. Currently Available Omega-3 Fatty Acid Products

Product (Generic Name)	Regulatory Status
Vascepa® (icosapent ethyl)	Prescription
Lovaza® (omega-3 acid ethyl esters)	Prescription
Fish oil (multiple product brands available)	Dietary supplement

Fish oils also contain omega-3 fatty acids and are available as dietary supplements. Although the FDA does regulate some aspects of dietary supplements, there are several important cautions:

- Manufacturers of fish oil supplements are not required to demonstrate that these products are safe or effective.
- There is substantial variability in content and purity among formulations of fish oil dietary supplements.
- Studies have found that some fish oil supplements contain impurities, including saturated fat and oxidized lipids, which could counteract any potential benefits associated with the products.²³

Due to these drawbacks, clinicians should not recommend dietary supplements. A recent AHA Scientific Advisory on hypertriglyceridemia also cautioned against use of dietary food supplements to treat hypertriglyceridemia.²⁴

Omega-3 Fatty Acids and CVD Risk

Studies investigating the use of omega-3 fatty acids to reduce CVD risk have revealed benefits associated with some of these products. The Japan EPA Lipid Intervention Study (JELIS), published in 2007, was the first study that demonstrated a benefit when an omega-3

Table 1. Historical Perspective

2010 to 2013	2015	2017 to 2018
<p>Several cardiovascular outcomes studies found no additional benefit in the primary cardiovascular endpoint when fenofibrate and niacin were added to a statin.</p> <ul style="list-style-type: none">• Action to Control Cardiovascular Risk in Diabetes [ACCORD] Lipid trial, using fenofibrate;• Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes [AIM-HIGH] trial, using niacin; and• The Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events [HPS2-THRIVE], using niacin. <p>A post-hoc analysis of subjects with elevated TGs and low high-density lipoprotein cholesterol (HDL-C) did find CVD benefit associated with niacin treatment in this high-risk subgroup.¹⁶⁻¹⁹ However, post-hoc analyses should be considered hypothesis-generating until a definitive study can be conducted.</p>	<p>The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) demonstrated that the addition of a cholesterol absorption inhibitor (ezetimibe) to a statin provided additional cardiovascular risk reduction benefits.²⁰</p>	<p>The ODYSSEY and Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trials have found that the proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors (evolocumab and alirocumab) also significantly improve cardiovascular outcomes, compared with statin treatment alone.^{21,22} Although LDL-C is the main target of ezetimibe and the PCSK9 inhibitors, these agents also have modest TG-lowering properties.</p>



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fatty acid product was added to a statin. JELIS assessed the effects of 1.8 g purified eicosapentaenoic acid (EPA) daily in a Japanese population of 18,645 patients with elevated cholesterol who were also taking a statin. In this study, the addition of EPA treatment was associated with a 19% reduction in the primary composite cardiovascular endpoint after a median of 4.6 years of follow-up.²⁵ In the primary prevention subgroup of subjects with high TGs and low HDL-C (TG ≥ 150 mg/dL and HDL-C < 40 mg/dL), which was a post-hoc analysis, there was a 53% relative risk reduction in CVD.²⁶

More recently, REDUCE-IT, published in 2019, evaluated IPE, which is also a highly purified EPA, 4 g/day vs. placebo for preventing cardiovascular events in statin-treated patients who had a TG level of 135–499 mg/dL and LDL-C level of 41–100 mg/dL at baseline. Both primary prevention patients (those with diabetes and no prior history of CVD events) and secondary prevention patients (those with a history of CVD events) were enrolled.¹ Patients were either 45 years of age or older with established CVD (defined as: documented coronary artery disease; prior ischemic stroke; carotid arterial stenosis; carotid revascularization; peripheral arterial disease), or were 50 years of age or older with diabetes mellitus and at least one additional risk factor [defined as: M ≥ 55 yo or F ≥ 65 yo; cigarette smoker; hypertension (SBP ≥ 140 , DBP ≥ 90 , or on antihypertensive medications); HDL-C ≤ 40 mg/dL in M or ≤ 50 mg/dL in F; Hs-CRP > 3.00 mg/L; renal dysfunction (CrCL > 30 and < 60 mL/min); retinopathy; micro- or macro-albuminuria; ankle-brachial index (ABI) < 0.9].

REDUCE-IT enrolled 8,179 patients followed for a median time frame of 4.9 years. The primary outcome measure was a composite of cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, or unstable angina requiring emergent hospitalization. Treatment with IPE reduced the risk of the primary outcome by 25% (Fig. 1) compared to placebo. The secondary endpoint was a composite of cardiovascular death, nonfatal MI, or nonfatal stroke, and was reduced by 26% in patients receiving IPE.²⁷ Total cardiovascular events were reduced by 30%.²⁸

Serious bleeding events occurred in 2.7% of the patients in the IPE group and in 2.1% in the placebo group (Fig. 2); although there was a trend toward statistical significance, this difference did not achieve statistical significance. There were no fatal bleeding events in either group. A significantly larger percentage of patients receiving IPE were hospitalized for atrial fibrillation or flutter, compared with placebo (3.1% vs. 2.1% of patients). However, incident stroke was reduced by 28% in IPE-treated patients.²⁷

Treatment Implications and a Look to the Future

REDUCE-IT is the first of several large clinical outcome trials evaluating patients with high TGs to be published. The data from REDUCE-IT suggest an important role of IPE in the treatment of patients with elevated TGs. However, the authors of REDUCE-IT caution, “The results of the current trial should not be generalized to other [omega-3] fatty acid preparations—in particular, dietary-supplement preparations of [omega-3] fatty acid mixtures, which are variable and unregulated and which have not been shown to have clinical benefit.”²⁷

Millions of patients in the U.S. fulfill the inclusion criteria for REDUCE-IT. Available data provide hope for these patients who have a high residual risk for CVD while receiving optimal treatment with a statin for elevated LDL-C. IPE is now indicated as an adjunct to maximally tolerated statin therapy to reduce the risk of CVD events in adult patients with elevated TGs (≥ 150 mg/dL) and established CVD or diabetes and 2 or more additional risk factors for CVD. As data from ongoing trials emerge, they will further inform the role of prescription omega-3 fatty acid products in preventing CVD.

Fig 1. Impact of IPE on Cardiovascular Outcomes

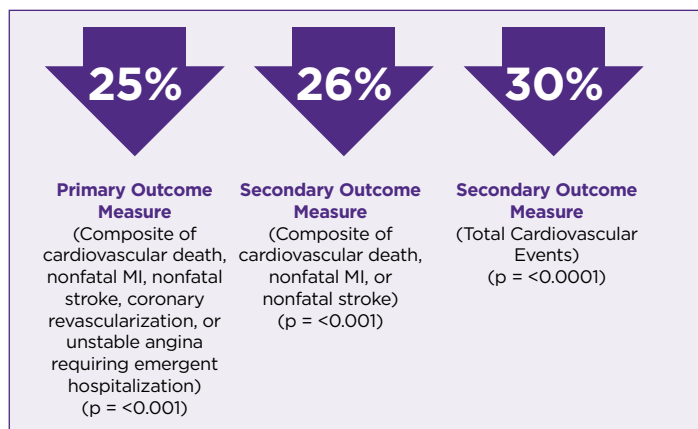
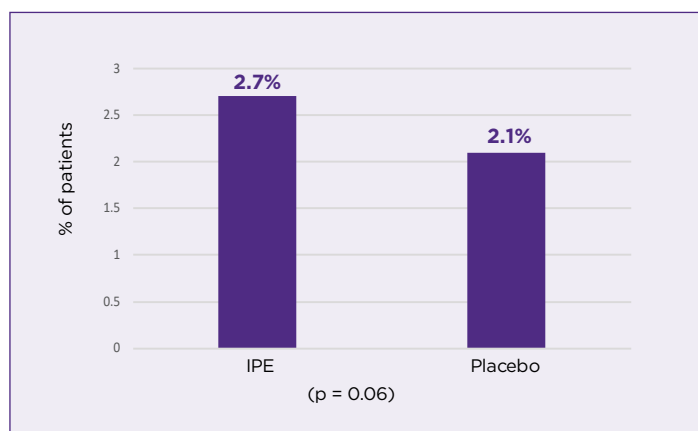


Fig 2. Rates of Serious Bleeding Events





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REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics—2020 Update: A report from the American Heart Association. *Circulation*. 2020;141(9):e139-e596.
2. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Amer Coll Cardiol*. 2018;73(24):e285-e350.
3. Miller M, Cannon CP, Murphy SA, et al.; PROVE IT-TIMI 22 Investigators. 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(7):724-730.
4. Toth PP, Philip S, Hull M, Granowitz C. Association of elevated triglycerides with increased cardiovascular risk and direct costs in statin-treated patients. *Mayo Clin Proc*. 2019;94(9):1670-1680.
5. Jacobson TA, Miller M, Schaefer EJ. Hypertriglyceridemia and cardiovascular risk reduction. *Clin Ther*. 2007;29(5):763-777.
6. Castelli WP. Epidemiology of triglycerides: a view from Framingham. *Am J Cardiol*. 1992;70(19):3H-9H.
7. Assmann G, Schulte H. The Prospective Cardiovascular Münster (PROCAM) study: prevalence of hyperlipidemia in persons with hypertension and/or diabetes mellitus and the relationship to coronary heart disease. *Am Heart J*. 1988;116(6 Pt 2):1713-1724.
8. Pedersen SB, Langsted A, Nordestgaard BG. Nonfasting mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis. *JAMA Intern Med*. 2016;176(12):1834-1842.
9. Kajikawa M, Maruhashi T, Kishimoto S, et al. Target of triglycerides as residual risk for cardiovascular events in patients with coronary artery disease—post hoc analysis of the FMD-J Study A. *Circ J*. 2019;83(5):1064-1071.
10. Klempfner R, Erez A, Sagit BZ, et al. Elevated triglyceride level is independently associated with increased all-cause mortality in patients with established coronary heart disease: twenty-two-year follow-up of the bezafibrate infarction prevention study and registry. *Circ Cardiovasc Qual Outcomes*. 2016;9(2):100-108.
11. Miller M, Stone NJ, Ballantyne C, et al.; American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2011;123(20):2292-2333.
12. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73(24):3168-3209.
13. Fan W, Philip S, Granowitz C, et al. Hypertriglyceridemia in statin-treated US adults: the National Health and Nutrition Examination Survey. *J Clin Lipidol*. 2019;13(1):100-108.
14. Tao Y, Xiong Y, Wang H, et al. APOC3 induces endothelial dysfunction through TNF- α and JAM-1. *Lipids Health Dis*. 2016;15(1):153.
15. Reiner Ž. Hypertriglyceridaemia and risk of coronary artery disease. *Nat Rev Cardiol*. 2017;14(7):401-411.
16. Ginsberg HN, Elam MB, Lovato LC, et al.; ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1563-1574.
17. Boden WE, Probstfield JL, Anderson T, et al.; AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365(24):2255-2267.
18. Landray MJ, Haynes R, Hopewell JC, et al.; HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014;371(3):203-212.
19. Guyton JR, Slee AE, Anderson T, et al. Relationship of lipoproteins to cardiovascular events: the AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes). *J Am Coll Cardiol*. 2013;62(17):1580-1584.
20. Cannon CP, Blazing MA, Giugliano RP, et al.; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387-2397.
21. Schwartz GG, Steg PG, Szarek M, et al.; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379(22):2097-2107.
22. Sabatine MS, Giugliano RP, Keech AC, et al.; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376(18):1713-1722.
23. Mason RP, Sherratt SCR. Omega-3 fatty acid fish oil dietary supplements contain saturated fats and oxidized lipids that may interfere with their intended biological benefits. *Biochem Biophys Res Commun*. 2017;483(1):425-429.
24. Skulas-Ray AC, Wilson PWF, Harris WS, et al.; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology. Omega-3 fatty acids for the management of hypertriglyceridemia: a science advisory from the American Heart Association. *Circulation*. 2019;140(12):e673-e691.
25. Yokoyama M, Origasa H, Matsuzaki M, et al.; Japan EPA Lipid Intervention Study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*. 2007;369(9567):1090-1098.
26. Saito Y, Yokoyama M, Origasa H, et al.; Japan EPA Lipid Intervention Study (JELIS) Investigators. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis*. 2008;200(1):135-140.
27. Bhatt DL, Steg PG, Miller M, et al.; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22.
28. Bhatt DL, Steg PG, Miller M, et al.; REDUCE-IT Investigators. Effects of icosapent ethyl on total ischemic events: from REDUCE-IT. *J Am Coll Cardiol*. 2019;73(22):2791-2802.

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