Current Cardiovascular Risk Reports (2019) 13: 6
https://doi.org/10.1007/s12170-019-0603-3

LIPIDS (E. MICHOS, SECTION EDITOR)

Triglycerides: Mendelian Randomization Studies Suggest Causal Role, but How to Treat in 2019?

Ji Eun Park[1] · Michael Miller[1,2,3]

Published online: 28 February 2019

Abstract

Purpose of Review Hypertriglyceridemia (HTG), defined by fasting levels at or exceeding 200 mg/dL, is characterized as a pro-inflammatory, pro-thrombotic, metabolic state associated with endothelial dysfunction, insulin resistance, type 2 diabetes mellitus (T2DM), and increased risk of cardiovascular disease (CVD). Mendelian randomization studies now support a causal role for TG-rich lipoproteins in CVD risk enhancement. Yet, until recently, only post-hoc analyses from clinical trials suggested that treating HTG would translate into reduced CVD risk.

Recent Findings The results of Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial demonstrated for the first time that patients with HTG and elevated CVD risk (i.e., pre-existing CVD or DM with additional risk factors) benefited after treatment with icosapent ethyl (IPE), a highly purified eicosapentanoic acid (EPA) taken 4 g daily. Ironically, the TG-lowering effect of IPE was relatively modest (20%), suggesting the interplay of other mechanisms beyond TG lowering that contributed to the robust benefits observed (25% relative risk reduction in the primary CVD endpoint). These mechanisms include downregulation of pro-inflammatory signaling pathways and restoration of endothelial dysfunction, cellular processes that are aggravated in HTG states. Consequently, high-risk patients with HTG should be considered for IPE therapy beyond traditional measures outlined in the 2018 American Heart Association/American College of Cardiology/Multi-Society Cholesterol Guidelines, pending the results of two ongoing clinical outcome trials, Statin Residual Risk Reduction with omega-3 carboxylic acids (Epanova®) in High Cardiovascular Risk Patients With Hypertriglyceridemia and Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients With Diabetes.

Summary Taken together, HTG reflects a highly atherogenic and pro-inflammatory state for which evidence-based therapy has now been demonstrated.

Keywords Hypertriglyceridemia · Cardiovascular disease · Icosapent ethyl · Mendelian randomization

Introduction

Triglycerides (TG) have long been known to be associated with an increased risk of cardiovascular disease (CVD). Borderline-elevated and high levels of hypertriglyceridemia (HTG) is defined by the American Heart Association (AHA) and National Lipid Association as 150–199 and 200–499 mg/dL, respectively [1, 2]. Most recently, the 2018 AHA/ACC/Multi-Society Cholesterol Guidelines defined moderate TG elevation as levels exceeding 175 mg/dL [3].

While elevated TG within the United States (U.S.) population may be declining, it continues to be a significant burden. For example, the National Health and Nutrition Examination Surveys (NHANES) from 1999 to 2004 found that the percentage of adults with TG levels above 150 mg/dL, 200 mg/dL, 500 mg/dL, and 1000 mg/dL approximates 33, 18, 1.7, and 0.4%, respectively in the USA [4]. In patients with CVD, the prevalence of elevated TG levels is even higher. Even among patients receiving statin therapy, there remains a considerable risk of coronary heart disease (CHD) [5] with recent

This article is part of the Topical Collection on *Lipids*

✉ Michael Miller
mmiller@som.umaryland.edu

[1] Division of Cardiovascular Medicine, University of Maryland Medical Center, Baltimore, MD, USA

[2] Division of Cardiovascular Medicine, Department of Medicine, University of Maryland School of Medicine, 110 S Paca St., Suite 7-124, Baltimore, MD 21201, USA

[3] Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD, USA

estimates that up to one-third of patients receiving statin therapy have residual TG levels exceeding 150 mg/dL [6].

Recently, a causal relationship between triglyceride-rich lipoproteins (TRLs) and CVD has been suggested. Here, we review increasing evidence in support of prioritizing TG, a proxy for TRL, in CVD risk assessment.

Triglycerides as an Independent Risk Factor of Coronary Heart Disease

The evidence supporting the association of TG with increased risk of CVD is substantial. In the largest meta-analysis assessing the association between TG and CVD risk in the western population (29 studies; 262,525 participants; 10,158 CVD cases), a comparison of those with top third of TG values versus bottom third showed a significant association of TG level with CVD risk (risk ratio 1.7), even after adjusting for age, sex, smoking, and lipid concentration, confirming a similar study in an Asian population [7, 8]. In a study of 13,953 young men with untreated hyperlipidemia, a decrease in TG levels after 5 years was associated with a decrease in CVD risk as compared to stable TG levels [9]. Additionally, higher TG levels have been shown to be associated with increased risk of all-cause mortality. As part of the Bezafibrate Infarction Prevention study (BIP), 22-year mortality data of 15,355 patients screened for the trial showed increasing risk for all-cause mortality with increasing fasting TG levels above 100 mg/dL [10].

In the Copenhagen General Population Study, in 58,547 individuals without prior CVD, diabetes mellitus (DM), or statin use, those who were not statin-eligible but with TG ≥ 264 mg/dL approached a 10-year risk of major adverse CVD events that were similar to those were statin-eligible (5.7% vs. 7.6%) [11]. Additionally, even with concurrent statin treatment, TG levels after acute coronary syndrome have been shown to be associated with short- and long-term risk of CVD, even after controlling for low density lipoprotein cholesterol (LDL-C) levels [12, 13].

Proposed Mechanisms of TG-Mediated CVD

The mechanism of TG-mediated pathways is influenced by pro-inflammatory pathways. When TG within TRLs are hydrolyzed, the resulting byproducts are cholesterol ester (CE)–enriched remnant particles. Not only do these CE-enriched particles upregulate the expression of pro-inflammatory signaling pathways, but they also can be taken up by vascular wall macrophages in an unregulated manner [14, 15]. A second pro-atherogenic mechanism is the contribution of apolipoprotein C3 (ApoC3), due in part to downregulation of lipoprotein lipase (LPL) and activation of adhesion molecule expression [16]. Moreover, the identification of a loss-of-function mutations in ApoC3 (R19X) in the Old Order Amish residing in Lancaster, Pennsylvania, was associated with low TG levels (median, 31 mg/dL) and reduced coronary calcification, and the TG and HDL working group of the Exome Sequencing Project found that several ApoC3 loss-of-function variants, including R19X mutations, also coincided with reduced CVD risk [17, 18].

Causal Relationship of TG and CHD

The most compelling data supporting TRL as directly causative in CVD is derived from Mendelian randomization studies. In an analysis approximating 20,000 patients with myocardial infarction (MI) and 50,000 controls, a one-standard deviation increment in TG correlated with a 54% increased risk of MI [19]. A study by Holmes et al. using weighted allele scores based on multiple single-nucleotide polymorphisms associated with TG found allele scores for TG were associated with CVD events (odds ratio 1.61, 1.62 for restricted and unrestricted allele scores) [20]. Overall, the results of Mendelian randomization studies supporting TRL as a causal biomarker for CVD are summarized in an excellent review [21]. In addition to Mendelian randomization studies and the aforementioned discussion of variants in ApoC3, strong associations also exist between other gene candidates affecting TG metabolism and risk of CVD. Principles among these are monogenic variants in *ANGPTL3, ANGPTL4, APOA5*, and *LPL* [15]. In one analysis studying genetic variants, a regulatory variant in ApoA5 was shown to be correlated to TG in a dose-dependent manner, per allele, suggesting TG-mediated pathways in CVD [22]. Another recent Mendelian randomization analysis identified 5 *LPL* gain-of-function variants to be associated with significant reductions in both TG and CHD risk [23••].

Clinical Trials of TG and CVD

While earlier clinical trials testing TG-lowering therapies [24–27] failed to demonstrate improvement in CVD risk despite significant reductions in TG, these studies were criticized because they did not primarily enroll patients with HTG. In fact, prior to REDUCE-IT (see below), purified EPA has been the only TG-lowering compound to demonstrate reduced CVD risk, albeit in a non-HTG population. Specifically, the open-label Japan EPA Lipid

Intervention Study (JELIS) found that addition of high-dose EPA (1.8 g) to statin therapy reduced the risk of CVD in those with total cholesterol > 250 mg/dL and median baseline TG of 154 mg/dL compared to controls [28]. A post-hoc analysis conducted in the subgroup of patients with baseline TG levels greater than 200 mg/dL with HDL-C less than 40 mg/dL found a 53% reduction in CVD risk in JELIS patients treated with EPA compared to no EPA [29]. It is noteworthy that outside of the JELIS study, other trials employing either unregulated dietary supplements or prescription EPA/docosahexaenoic acid (DHA) at low dosages (e.g., 1 g daily) have been negative vis-à-vis reduction in CVD risk [27, 30, 31••].

Consequently, the results of JELIS set the stage for further study investigating patients with HTG. The first clinical outcome study was the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) [31••]. In REDUCE-IT, 8179 patients with elevated TG (initially, 150–500 mg/dL followed by protocol amendment to 200–500 mg/dL) and CVD or high risk primary prevention (i.e., DM treated with medication, age > 50 years and at least 1 additional CVD risk factor) on statin therapy were randomized to receive 2 g of icosapent ethyl (IPE) twice a day or a mineral oil placebo [32]. The study population was primarily a secondary prevention cohort, with 70.7% of participants having established CVD. Baseline characteristics included a majority of patients with T2DM (58%), a sizeable percentage of women (28–29%) with elevated TG (median, 216–217 mg/dL) and well-controlled statin-treated levels of LDL-C (median, 74–76 mg/dL). At 4.9 years, there was a 20% reduction in TGs and 25% lower risk of the primary end point (CVD death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina) in the IPE-treated group compared to placebo, confirming the results of the JELIS trial, with the additional benefit of decreased CVD death [33••]. There was also a 25% reduction in risk for the secondary endpoint, a composite of CVD death, nonfatal MI, or nonfatal stroke, in the IPE-treated group compared to placebo. Uniquely, the hierarchical testing of endpoints and the rates of ischemic end points, with the exception of death from any cause, were significantly lower in the IPA-treated group than in the placebo group. A tertiary endpoint of hospitalization for atrial fibrillation or flutter and serious, non-fatal bleeding rate was higher in the IPE-treated group than in placebo patients.

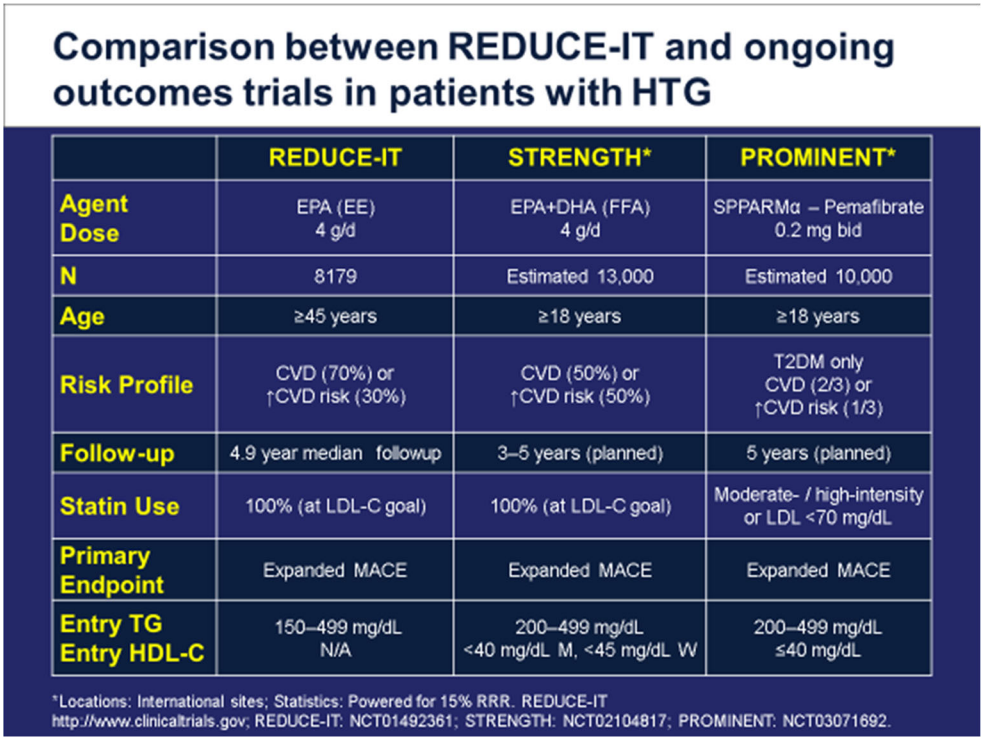
Interestingly, the results of REDUCE-IT begets the question as to whether (1) the effect is unique to IPE compared to the combination of EPA/DHA preparations and/or lower doses used in prior studies (1 g/day) versus JELIS (1.8 g/day) and REDUCE-IT (4 g/day) or (2) whether mineral oil was not the appropriate comparator [34]. As noted above, the CVD benefit of IPE, a highly concentrated and purified form of EPA that was used in REDUCE-IT, was considerably greater than that predicted by the 20% lowering effect on TG alone. This is consistent with intracellular pleiotropic properties that are analogous and potentially synergistic with statins. They include downregulation of inflammatory signaling pathways, normalization of endothelial function, and inhibition of LDL oxidation previously demonstrated with IPE [35–37]. With respect to mineral oil, the modest 5 mg/dL differential in LDL-C between groups could not account for the sizeable reduction in CHD events observed (25%) in the primary endpoint. Moreover, there was no difference in CHD risk among mineral oil–treated placebo patients with or without an increase in LDL-C. We await the outcome of two additional clinical outcome trials in patients with HTG. They are the Statin Residual Risk Reduction with omega-3 carboxylic acids (Epanova®) in High Cardiovascular Risk Patients With Hypertriglyceridemia (STRENGTH) (ClinicalTrials.gov number, NCT02104817) and the fibrate, Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients With Diabetes (PROMINENT) (ClinicalTrials.gov identifier: NCT03071692). A comparison between REDUCE-IT and the ongoing clinical outcomes trials is shown in the Table.

Two additional ongoing studies testing EPA are the Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy–Statin and Eicosapentaenoic Acid (RESPECT-EPA), a secondary prevention assessment of CVD events in a Japanese cohort receiving statin therapy (UMIN clinical trials registry number, UMIN000012069) and the Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy–Statin and Eicosapentaenoic Acid (EVAPORATE), evaluating the effect of the IPE compound, Vascepa® on progression of coronary atherosclerosis in persons with elevated triglycerides (200–499) [38].

Based on the results of REDUCE-IT, we recommend the following for CVD patients with HTG. After lifestyle [1] and statin therapy, IPE represents the most logical choice for second-line treatment if residual TG elevation persists (e.g., 150–499 mg/dL). Fibrates are reserved as third-line therapy based upon the post-hoc analysis in the ACCORD-Lipid study that suggested clinical benefit [39]. If a fenofibrate is used with a statin, fenofibrate is preferred over gemfibrozil due to safety concerns when the latter is combined [2, 3]. At this time, there is no clinical outcome evidence to support using EPA/DHA in prescription or in dietary supplement form [3].

Conclusion and Summary

In summary, there is mounting evidence supporting a causal role for TRL in CVD risk assessment. The favorable results of



REDUCE-IT indicate that high doses of purified EPA reduce CVD outcomes in patients with HTG, despite therapeutic levels of LDL-C on concomitant statin therapy. Ongoing trials will help to further clarify the extent to which other compounds that lower TG may also favorably translate into reduced CVD risk.

Compliance with Ethical Standards

Conflict of Interest Dr. Miller is a consultant for Amarin and serves on the Steering Committee for the REDUCE-IT Study. Dr. Park has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects for which either co-author served as site investigator.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011;123:2292–333.
2. Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, et al. National Lipid Association Recommendations for patient-centered management of dyslipidemia: part 1—full report. J Clin Lipidol. 2015;9:129–69.
3. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary. J Am Coll Cardiol. 2018:25708. https://doi.org/10.1016/j.jacc.2018.11.002.
4. Ford ES, Li C, Zhao G, Pearson WS, Mokdad AH. Hypertriglyceridemia and its pharmacologic treatment among US adults. Arch Intern Med. 2009;169:572–8.
5. Grundy SM, Cleeman JI, Merz CNB, Brewer HB Jr, Clark LT, Hunninghake DB, et al. National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, American Heart Association implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. Circulation. 2004;110:227–39.
6. Fan W, Philip S, Granowitz C, Toth PP, Wong ND. Hypertriglyceridemia in statin-treated US adults: the National Health and Nutrition Examination Survey. J Clin Lipidol 2018; In Press.
7. Patel A, Barzi F, Jamrozik K, Lam TH, Ueshima H, Whitlock G, et al. Asia Pacific cohort studies collaboration. Serum triglycerides as a risk factor for cardiovascular diseases in the Asia-Pacific region. Circulation. 2004;110:2678–86.
8. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, et al. Triglycerides and the risk of coronary heart disease: 10 158 incident cases among 262 525 participants in 29 Western prospective studies. Circulation. 2007;115:450–8.
9. Tirosh A, Rudich A, Shochat T, Tekes-Manova D, Israeli E, Henkin Y, et al. Changes in triglyceride levels and risk for coronary heart disease in young men. Ann Intern Med. 2007;147:377–85.
10. Klempfner R, Erez A, Sagit B-Z, Goldenberg I, Fisman E, Kopel E, 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;9:100–8.
11. Madsen CM, Varbo A, Nordestgaard BG. Unmet need for primary prevention in individuals with hypertriglyceridaemia not eligible for statin therapy according to European Society of Cardiology/European Atherosclerosis Society guidelines: a contemporary population-based study. Eur Heart J. 2018;39:610–9.
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;51:724–30.
13. Schwartz GG, Abt M, Bao W, DeMicco D, Kallend D, Miller M, et al. Fasting triglycerides predict recurrent ischemic events in patients with acute coronary syndrome treated with statins. J Am Coll Cardiol. 2015;65:2267–75.
14. Nakamura T, Takano H, Umetani K, Kawabata KI, Obata JE, Kitta Y, et al. Remnant lipoproteinemia is a risk factor for endothelial vasomotor dysfunction and coronary artery disease in metabolic syndrome. Atherosclerosis. 2005;181:321–7.
15. Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. J Am Coll Cardiol. 2018;72:330–43.
16. Caron S, Staels B. Apolipoprotein CIII: a link between hypertriglyceridemia and vascular dysfunction? Circ Res. 2008;103:1348–50.
17. Pollin TI, Damcott CM, Shen H, Ott SH, Shelton J, Horenstein RB, et al. A null mutation in human APOC3 confers a favorable plasma lipid profile and apparent cardioprotection. Science. 2008;322:1702–5.
18. Crosby J, Peloso GM, Auer PL, et al. 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;371:22–31.
19. Musunuru K, Kathiresan S. Surprises from genetic analyses of lipid risk factors for atherosclerosis. Circ Res. 2016;118:579–85.
20. Holmes MV, Asselbergs FW, Palmer TM, Drenos F, Lanktree MB, Nelson CP, et al. Mendelian randomization of blood lipids for coronary heart disease. Eur Heart J. 2015;36:539–50.
21. Khera AV, Kathiresan S. Genetics of coronary artery disease: discovery, biology and clinical translation. Nat Rev Genet. 2017;18:331–4.
22. Sarwar N, Sandhu MS, Ricketts SL, et al. Triglyceride coronary disease genetics consortium and emerging risk factors collaboration, Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. Lancet. 2010;375:1634–9.
23.•• Ference BA, JJP K, Ray KK, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. JAMA. 2019;321(4):364–73 **This Mendelian randomization analysis of 654,783 subjects found that the absolute change in apoB due to genetic variants causing low TG or low LDL-C was correlated to similar reductions in CHD risk**.
24. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al. FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366:1849–61.
25. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563–74.
26. Guyton JR, Slee AE, Anderson T, Fleg JL, Goldberg RB, Kashyap ML, 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;62:1580–4.
27. ASCEND study collaborative group, Bowman L, Mafham M, Wallendszus K, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. N Engl J Med. 2018;379:1540–50.
28. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007;369:1090–8.
29. Saito Y, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Ishikawa Y, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: subanalysis of primary prevention cases from the Japan EPA lipid intervention study (JELIS). Atherosclerosis. 2008;200:135–40.
30. Aung T, Halsey J, Kromhout D, Gerstein HC, Marchioli R, Tavazzi L, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77 917 individuals. JAMA Cardiol. 2018;3:225–34.
31.•• Manson JE, Cook NR, Lee I-M, et al. Marine n− 3 fatty acids and prevention of cardiovascular disease and cancer. N Engl J Med. 2019;380:23–32 **Manson et al. examined marine derived omega-e fatty acids (1 gram daily) in men and women (aged 50 and 55 years or older respectively) who were free of CVD at baseline. After a median followup period of 5.3 years there were no differences in major CVD events between groups, consistent with prior data suggesting that low dose omega-3 fatty acids is ineffective in CVD risk reduction**.
32. Bhatt DL, Steg PG, Brinton EA, Jacobson TA, Miller M, Tardif JC, et al. Rationale and design of REDUCE-IT: reduction of cardiovascular events with icosapent ethyl-intervention trial. Clin Cardiol. 2017;40:138–48.
33.•• Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019;380:11–22 **Bhatt et al, examined 8179 patients with TG 135–500 mg/dL and high CVD risk (secondary prevention population 70.7%) assigned to icosapent ethyl 4 grams daily or placebo. Over a median 4.9 years, the primary endpoint (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina) was significantly reduced by 25%. The 20% reduction in CV death is the first lipid-based trial to demonstrate such benefit in statin-treated patients**.
34. Kastelein JJP, Stroes ESG. FISHing for the miracle of eicosapentaenoic acid. N Engl J Med. 2018;380:89–90.
35. Borow KM, Nelson JR, Mason RP. Biologic plausibility, cellular effects, and molecular mechanisms of eicosapentaenoic acid (EPA) in atherosclerosis. Atherosclerosis. 2015;242:357–66.
36. Mason RP, Dawoud H, Jacob RF, Sherratt SCR, Malinski T. Eicosapentaenoic acid improves endothelial function and nitric oxide bioavailability in a manner that is enhanced in combination with a statin. Biomed Pharmacother. 2018;103:1231–7.
37. Mason RP, Sherratt SCR, Jacob RF. Eicosapentaenoic acid inhibits oxidation of ApoB-containing lipoprotein particles of different size in vitro when administered alone or in combination with atorvastatin active metabolite compared with other triglyceride-lowering agents. J Cardiovasc Pharmacol. 2016;68:33–40.
38. Budoff M, Brent Muhlestein J, Le VT, May HT, Roy S, Nelson JR. Effect of Vascepa (icosapent ethyl) on progression of coronary atherosclerosis in patients with elevated triglycerides (200–499 mg/dL) on statin therapy: rationale and design of the EVAPORATE study. Clin Cardiol. 2018;41:13–9.
39. Elam M, Lovato L, Ginsberg H. The ACCORD-lipid study: implications for treatment of dyslipidemia in type 2 diabetes mellitus. Clin Lipidol. 2011;6:9–20.