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JACC REVIEW TOPIC OF THE WEEK

Unmet Need for Adjunctive Dyslipidemia Therapy in Hypertriglyceridemia Management

Om P. Ganda, MD,[a] Deepak L. Bhatt, MD, MPH,[b] R. Preston Mason, PhD,[c] Michael Miller, MD,[d] William E. Boden, MD[e]

ABSTRACT

Despite the important role of high-intensity statins in reducing atherosclerotic cardiovascular disease events in secondary and primary prevention, substantial residual risk persists, particularly among high-risk patients with type 2 diabetes mellitus, metabolic syndrome, and obesity. Considerable attention is currently directed to the role that elevated triglycerides (TGs) and non–high-density lipoprotein cholesterol levels play as important mediators of residual atherosclerotic cardiovascular disease risk, which is further strongly supported by genetic linkage studies. Previous trials with fibrates, niacin, and most cholesterol ester transfer protein inhibitors that targeted high-density lipoprotein cholesterol raising, and/or TG lowering, have failed to show conclusive evidence of incremental event reduction after low-density lipoprotein cholesterol levels were "optimally controlled" with statins. Although omega-3 fatty acids are efficacious in lowering TG levels and may have pleiotropic effects such as reducing plaque instability and proinflammatory mediators of atherogenesis, clinical outcomes data are currently lacking. Several ongoing randomized controlled trials of TG-lowering strategies with an optimal dosage of omega-3 fatty acids are nearing completion. (J Am Coll Cardiol 2018;72:330–43) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

CASE SCENARIO

A 58-year-old obese male patient with type 2 diabetes mellitus (T2DM) presents with a history of acute coronary syndrome and previous coronary artery bypass grafting 2 years earlier. His glycosylated hemoglobin value has been stable at 7.2% with metformin and liraglutide 1.8 mg daily. He is currently normotensive with lisinopril/hydrochlorothiazide 20 mg/12.5 mg with a urine/albumin creatinine ratio at 80 μg/mg and an estimated glomerular filtration rate of 48 ml/min. The patient's current lipid profile with rosuvastatin 40 mg and ezetimibe 10 mg daily is as follows: low-density lipoprotein cholesterol (LDL-C), 66 mg/dl; triglycerides (TGs), 320 mg/dl; high-density lipoprotein cholesterol (HDL-C), 38 mg/dl; and non-HDL-C, 130 mg/dl. The patient and his primary care physician are concerned about his residual risk of recurrent atherosclerotic cardiovascular disease (ASCVD) events and his overall prognosis.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Clinical Research and Adult Diabetes Sections, Joslin Diabetes Center, Harvard Medical School, Boston, Massachusetts; [b]Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, Massachusetts; [c]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [d]Cardiovascular Division, Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland; and the [e]VA New England Healthcare System, Boston University School of Medicine, Boston, Massachusetts. Dr. Ganda is partially supported by the National Institute of Diabetes and Digestive and Kidney Diseases grant no. P30-DK036836; has served as a consultant/advisory board member for Sanofi-Regeneron, Amarin, Merck, and Novo Nordisk; has received honoraria from Merck, Novo Nordisk, and Sanofi-Regeneron; and has received a research grant from Amarin Pharma. Dr. Bhatt has served on the advisory board for Cardax, Elsevier PracticeUpdate Cardiology, Medscape Cardiology, and Regado Biosciences; has served on the board of directors for Boston VA Research Institute and Society of Cardiovascular Patient Care; chair for the American Heart Association Quality Oversight Committee; member of the data monitoring committees for the Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, and Population Health Research Institute; has received honoraria from the American College of

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INTRODUCTION

ASCVD continues to be the leading cause of death and disability worldwide (1). In the United States alone, >18 million Americans have coronary heart disease (CHD), and despite profound advances in management, both morbidity and mortality persist (2). Elevated levels of LDL-C are an established predictor of the risk of incident CHD events and have been the principal target of dyslipidemia treatment efforts for the past 3 decades. Multiple primary and secondary prevention trials have shown a significant reduction of 25% to 35% in the risk of cardiovascular events with statin therapy (3–5). However, residual risk persists despite the achievement of target LDL-C levels, often defined as <70 mg/dl (4) (**Central Illustration**).

Epidemiological studies have shown that, in addition to elevated LDL-C levels, both elevated baseline levels of TGs and low levels of HDL-C are independent predictors of the risk of CHD (6,7). However, even among patients treated with high-intensity statins, residual risk persists, particularly in high-risk subjects with pre-existing ASCVD, T2DM, or metabolic syndrome (5,8). The prevalence of T2DM and metabolic syndrome, as well as obesity, has been increasing at an alarming rate, particularly over the last few decades. This constellation of high-risk clinical conditions encompasses a phenotype that promotes a proinflammatory state with both atherogenic dyslipidemia (elevated TG levels with or without low HDL-C levels) and dysglycemia, which together conspire to increase the risk for subsequent adverse cardiovascular events (9,10). However, despite intensive treatment with statins and newer therapies directed at more rigorous reductions in LDL-C levels, the fundamental atherogenic dyslipidemia described here that is common to both T2DM and metabolic syndrome is not fully ameliorated by treatments directed at LDL-C reductions alone.

EPIDEMIOLOGY OF DYSLIPIDEMIA (HIGH TG AND LOW HDL-C) AND ASCVD RISK

Hypertriglyceridemia is a highly prevalent lipid disorder in the adult population. According to recent estimates from the U.S. National Health and Nutrition Examination Survey (1999 to 2014) in adults ≥20 years of age, there have been gradual declines in the prevalence of LDL-C as well as TG, largely due to the use of lipid-lowering medications (11). However, the prevalence of TG levels ≥150 mg/dl was approximately 25%, and the prevalence of high TG levels is likely to keep increasing as the triple epidemics of obesity, metabolic syndrome, and T2DM continue to escalate globally. In addition to the estimated ~30 million adults with T2DM in the United States and ~415 million worldwide (12), an almost 3-fold

ABBREVIATIONS AND ACRONYMS

ANGPTL = angiopoietin-like protein
apo = apolipoprotein
ASCVD = atherosclerotic cardiovascular disease
CETP = cholesteryl ester transfer protein
CHD = coronary heart disease
CI = confidence interval
CRP = C-reactive protein
DHA = docosahexaenoic acid
EPA = eicosapentaenoic acid
HDL-C = high-density lipoprotein cholesterol
HR = hazard ratio
IL = interleukin
LDL-C = low-density lipoprotein cholesterol
OM3FA = omega-3 fatty acids
OR = odds ratio
RCT = randomized controlled trial
RR = relative risk
T2DM = type 2 diabetes mellitus
TG = triglyceride

Cardiology (senior associate editor, *Clinical Trials and News*, ACC.org), Belvoir Publications (Editor-in-Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor-in-Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor, associate editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (secretary/treasurer), and WebMD (CME steering committees); Clinical Cardiology (deputy editor), NCDR-ACTION Registry Steering Committee (chair), VA CART Research and Publications Committee (chair); has received research funding from Abbott, Amarin (including for his role as chair and principal investigator of REDUCE-IT [Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention] trial), Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Regeneron, Roche, Sanofi-Aventis, and The Medicines Company; has received royalties from Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); has served as site co-investigator for Biotronik, Boston Scientific, St. Jude Medical (now Abbott), and Svelte; has served as a trustee for the American College of Cardiology; and unfunded research for FlowCo, Merck, PLx Pharma, and Takeda. Dr. Mason has received grant/research support from Amarin, Amgen, Pfizer, and Novartis; and provides speaking and consultancy services (including receipt of honoraria) for Pfizer and Amarin Pharma Inc.; Dr. Mason donates all honoraria to charity. Dr. Miller has served on an American College of Cardiology, nutrition workgroup (JACC: Section Editor, Clinical Trials and Registries); American Heart Association, Chair, ATVB Council on Clinical Lipidology; member, Council on Lifestyle and Cardiometabolic Health; Akcea Therapeutics, consultant; Amarin, consultant and advisor, steering committee member of REDUCE-IT trial; AstraZeneca, trustee, Connection for Cardiovascular Health Foundation; and author, "Heal Your Heart" (Rodale Press) (author royalties donated to the American Heart Association). Dr. Boden has received research grant support from Clinical Trials Network, Massachusetts Veterans Epidemiology, Research, and Information Center (MAVERIC), VA New England Healthcare System, NHLBI as national co-principal investigator for the ISCHEMIA Trial, Axio Research, Inc., AbbVie, Amarin Pharmaceuticals. Inc., Amgen, AstraZeneca, and Sanofi; has served on the board of directors for Boston VA Research Institute, Inc., CardioDx; has served on the data monitoring committee for VA Cooperative Studies Program; was national coordinator for the STRENGTH Trial, with honoraria from the Cleveland Clinic Clinical Coordinating Center; and has received speaking honoraria from Amgen, Aralez Pharmaceuticals, AstraZeneca, Janssen/Johnson & Johnson, and Regeneron.

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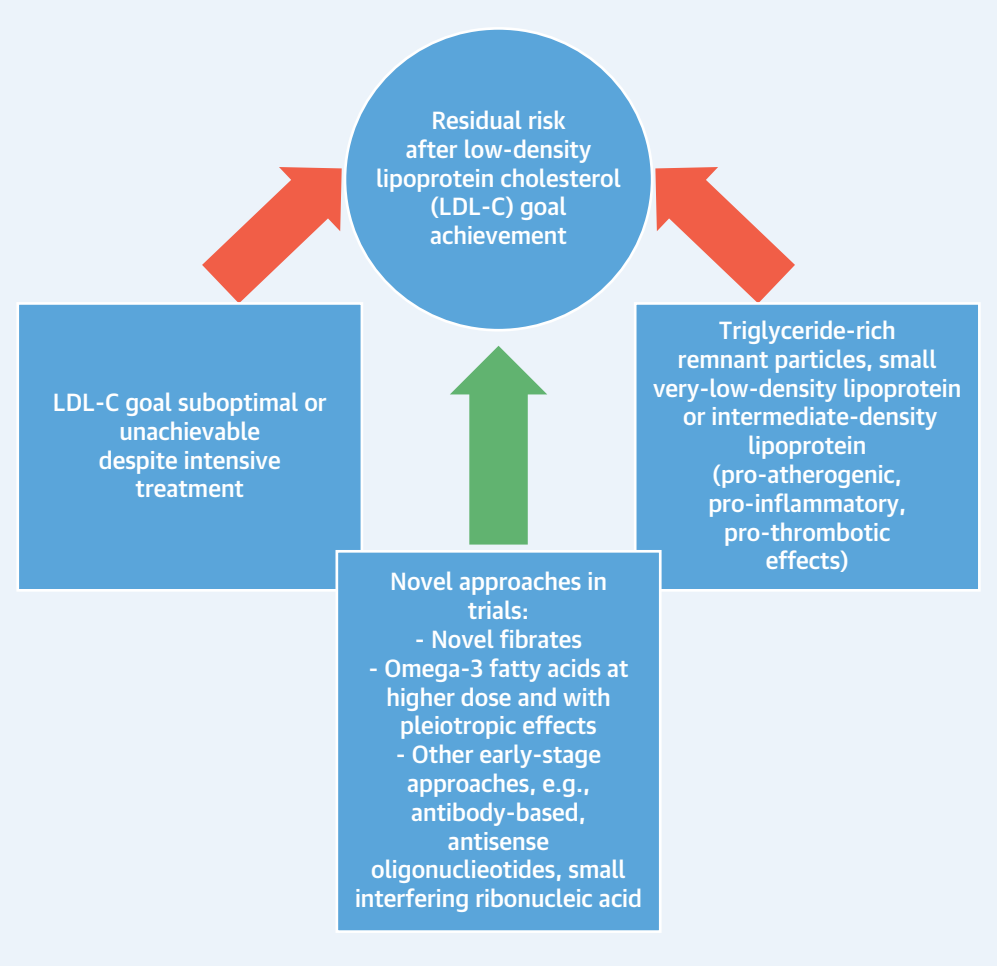
CENTRAL ILLUSTRATION **Promising Therapies for Hypertriglyceridemia**



Ganda, O.P. et al. J Am Coll Cardiol. 2018;72(3):330–43.

Proposed mechanisms underlying residual risk of atherosclerotic cardiovascular disease events after optimal statin treatment, role of triglyceride-rich lipoproteins, and potential treatment approaches. LDL-C = low-density lipoprotein cholesterol.

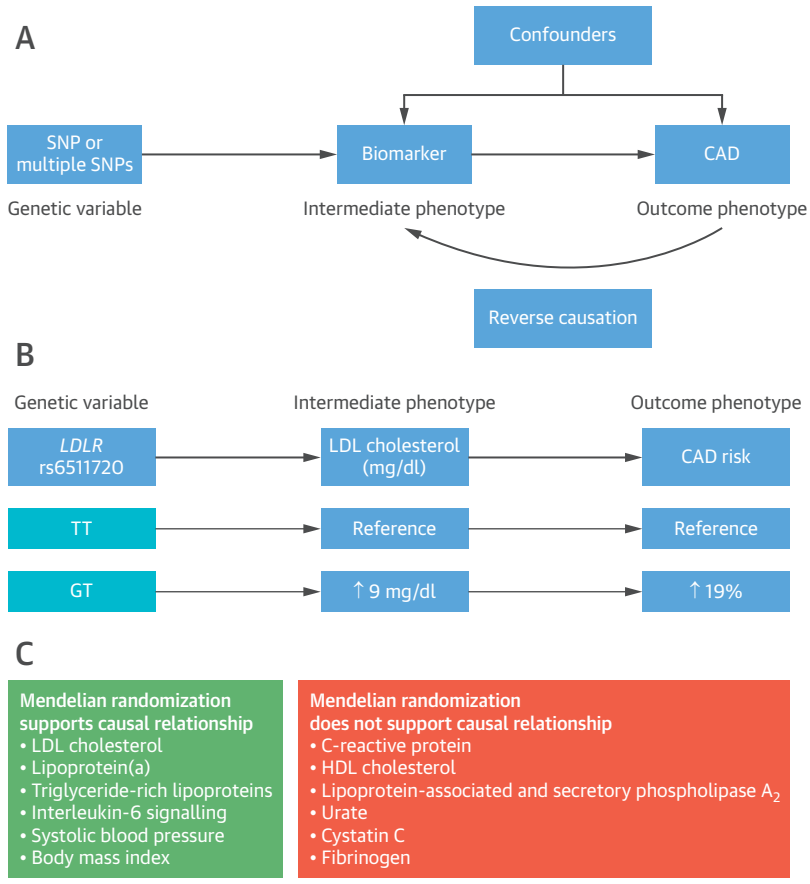
higher rate of individuals with prediabetes has been reported in the last few decades (13), and prediabetes is associated with insulin resistance and metabolic syndrome. This clinical phenotype is characterized by the aforementioned atherogenic dyslipidemia of elevated levels of TG, low HDL-C levels, and small dense LDL particles along with visceral obesity and nonalcoholic fatty liver disease. Thus, insulin resistance plays a major role in mediating the pathogenesis of metabolic syndrome (14).

Importantly, substantial residual risk of ASCVD events persists despite intensive statin therapy (4,8) and has prompted a re-assessment of the role of other lipoproteins as incremental risk predictors. Meta-analyses of long-term prospective studies have reported an association between elevated TG levels and ASCVD (6,7), although this association is attenuated after adjustment for HDL-C level, as these 2 lipid parameters are highly inversely correlated.

GENETIC LINKAGE BETWEEN DYSLIPIDEMIA AND INCIDENT ASCVD RISK

The mechanism(s) linking TG elevation and atherogenesis have been a topic of conflict because not all TG particles are atherogenic. Large TG-rich remnant particles are unable to penetrate the vessel wall (15,16).

FIGURE 1 Summary of Mendelian Randomization Studies to Identify Causal Biomarkers for Risk of ASCVD



(A to C) Depictions of various examples of genetic polymorphisms affecting major lipoproteins, and other risk factors, and their relationships with ASCVD outcomes. ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein; SNP = single-nucleotide polymorphism. Reproduced with permission from Khera and Kathiresan (21).

However, because TGs are hydrolyzed from TG-rich particles, their cholesteryl ester–enriched byproducts (e.g., chylomicron and very-low-density lipoprotein remnants and smaller very-low-density lipoprotein particles) can promote atherogenesis via multiple mechanisms, including infiltration into the vessel wall or via proinflammatory and prothrombotic pathways (7,17). In a recent post hoc analysis from the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial (18), there was a strong association between the smallest, but not larger, TG particles, on statin treatment and primary cardiovascular endpoints (adjusted hazard ratio [HR]: 1.68; confidence interval [CI]: 1.28 to 2.22).

TG levels, as with other lipids, are highly dependent on genetic factors, accentuated by environmental factors such as lifestyle, obesity, and certain drugs. Hypertriglyceridemia, in most cases, is a polygenic disorder and is linked with a smaller number of several monogenic traits (7,19,20). The most persuasive evidence for a causative role of hypertriglyceridemia, rather than low HDL-C level, in ASCVD comes from recent genetic linkage studies. In a large Mendelian analysis involving ~20,000 cases with myocardial infarction and ~50,000 control subjects, a 1 SD increase in LDL-C level was associated with a highly significant 113% increase, and a 1 SD increase in TG levels was associated with a highly significant 54% increase, in risk for myocardial infarction (20). However, there was no risk association with low baseline levels of HDL-C, as noted in earlier studies (21). **Figure 1** summarizes the multiple Mendelian randomization studies to identify causal biomarkers for risk of ASCVD.

Consistent with genetic associations of elevated baseline TG levels and increased ASCVD events, a

similarly strong association has been reported with monogenic variants involving lipoprotein lipase (22), apolipoprotein (apo) A5 (23), apo CII (24), apo CIII (23,25,26), angiopoietin-like protein (ANGPTL) 3 (25,27,28), and ANGPTL4 (29). However, interpretation of genetic linkage studies may be complicated by other pleiotropic effects in lipoprotein subparticles. As an example, in the apo A5 variant (−1131T>C; rs 662799) (27), the association of ASCVD events with elevated TG levels was also accompanied by elevations in LDL/apo B and, in a small subset studied by using nuclear magnetic resonance imaging, by increased particle number and small, dense LDL (30). In summary, although overall genetic analyses strongly support the role of TG-rich particles in atherogenesis, they also highlight certain limitations in their interpretation (18,25,31).

In a large consortium of patients with ASCVD and control subjects, apo CIII mutations that were associated with lower CIII levels translated into reduced incident CHD risk (odds ratio: 0.60; 95% confidence interval [CI]: 0.47 to 0.75; $p = 4 \times 10^{6}$) (25). Very similar results were obtained from another large cohort in which apo CIII mutations leading to a 40% reduction in TG levels were associated with a 41% reduction in ASCVD (HR: 0.59; 95% CI: 0.41 to 0.386; $p = 0.007$) (26).

RANDOMIZED CONTROLLED TRIALS OF HDL-C RAISING AND TG LOWERING AND ASCVD EVENT REDUCTION

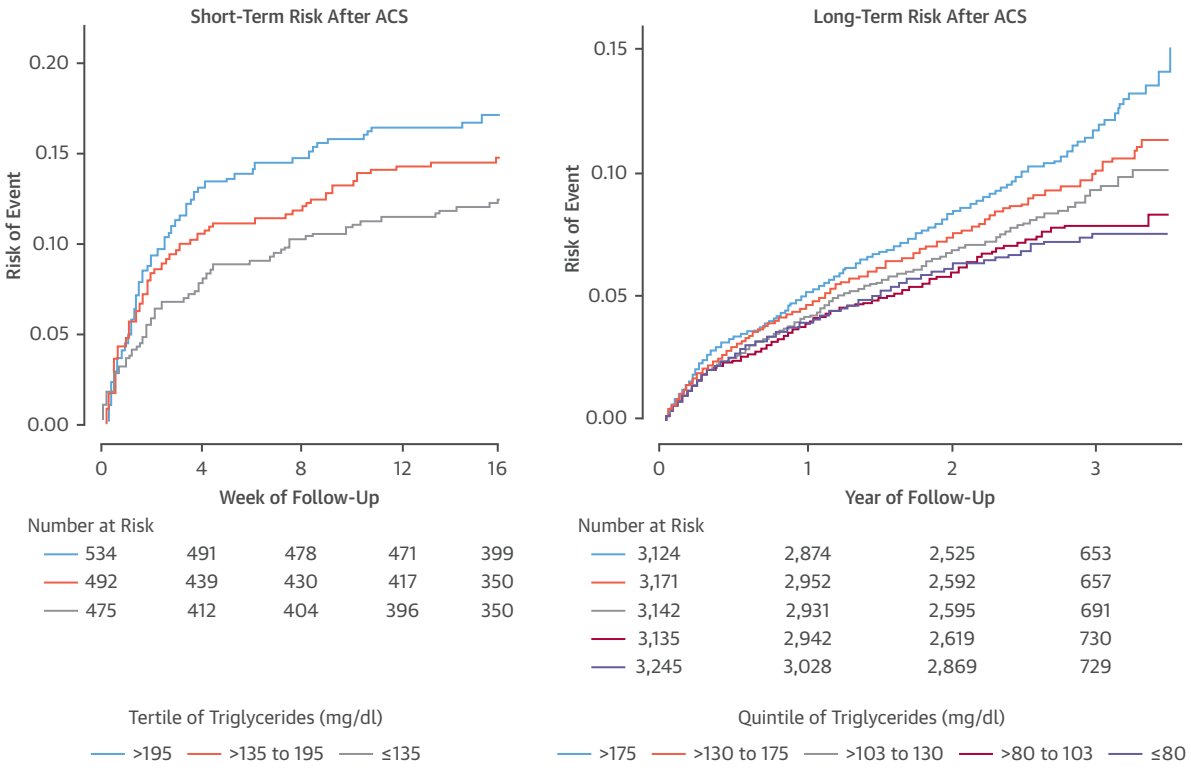
To assess the association between raising low levels of HDL-C and reducing CHD events, 2 large randomized controlled trials (RCTs) that used optimal statin therapy plus extended-release niacin or placebo failed to show a reduction in clinical event rates (32,33). In addition, 3 large RCTs evaluating different cholesteryl ester transfer protein (CETP) inhibitors (torcetrapib, dalcetrapib, and evacetrapib) failed to show reductions in ASCVD event rates, despite increasing HDL-C levels by up to 133%; in a fourth CETP inhibitor trial with anacetrapib, the impact on the primary endpoint was statistically modest and unrelated to the robust increase in HDL-C level (34). One potentially important caveat is that all of the CETP trials and 1 of the niacin trials (33) included patients who were not pre-selected for low baseline HDL-C levels. Thus, it remains unclear whether patient selection factors or interventions targeting HDL-C elevations may have led to these negative findings in statin-treated patients.

Regarding the impact of elevated TG levels in RCTs, the CTT (Cholesterol Treatment Trialists) meta-analysis of 14 statin trials showed that, in the T2DM subgroup (n = 18,686; mean follow-up: 4.3 years), there was a 26% higher rate of ASCVD events in the highest TG tertile 3 versus 1 (mean ≥2.0 mmol/l vs. <1.4 mmol/l) (35). These differences persisted in the statin-treated group (32.3% higher event rates in tertile 3 vs. 1). In the ACCORD (Action to Control Cardiovascular Risk in Diabetes)-Lipid trial, the event rates in those with TG tertile 3 vs. tertiles 1 + 2 (≥204 mg/dl vs. ≤ 203 mg/dl) were 21.9% higher in the control group taking statins alone, compared with those taking statins plus fenofibrate, after a mean follow-up of 4.7 years (36).

A more pronounced effect of elevated TG was reported in intensive LDL-lowering trials. In the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial of 4,162 patients with acute coronary syndromes, randomized to receive either atorvastatin 80 mg or pravastatin 40 mg, those with baseline TG levels <150 mg/dl (compared with ≥150 mg/dl) had significantly lower event rates after covariate adjustments (HR: 0.80; 95% CI: 0.6 to 0.97; $p = 0.025$) (37). These differences were also significant among those achieving LDL-C levels <70 mg/dl (HR: 0.72; 95% CI: 0.54 to 0.94; $p < 0.02$). Further analysis revealed a 1.4% reduction in major cardiovascular events by every 10 mg/dl on-treatment decrement in TG, after multiple adjustments including LDL-C and non-HDL-C. PROVE-IT results are also supported by 2 short- and long-term post-acute coronary syndromes trials, MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) and dal-OUTCOMES, respectively. In both studies, fasting TG levels were associated with subsequent primary outcomes, after multiple adjustments, including LDL-C and HDL-C (38). The MIRACL study included atorvastatin 80 mg (HR: 1.50 [$p < 0.03$] for TG >195 mg/dl vs. ≤135 mg/dl) and dal-OUTCOMES included dalcetrapib (HR: 1.61 [$p < 0.001$] for TG >175 mg/dl vs. ≤80 mg/dl) (**Figure 2**).

Finally, in a recent meta-regression analysis of 33 statin and nonstatin trials, 9 trials with fibrates revealed a greater benefit in ASCVD event reduction compared with the same LDL-C reduction with statins (observed relative risk [RR]: 0.88 [95% CI: 0.83 to 0.92]; expected RR: 0.94 [95% CI: 0.93 to 0.94]; $p = 0.02$) (39). However, the relationship was closer than expected, compared with the RR reduction of non-HDL-C instead of LDL-C (0.80 [95% CI: 0.77 to 0.82] and 0.77 [95% CI: 0.71 to 0.84]). These observations suggest that non-HDL-C may be a better lipid biomarker when assessing risk reduction in subjects with hypertriglyceridemia, but this theory requires further study.

FIGURE 2 **TG Levels and Risk After ACS**



Kaplan-Meier analysis of coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, cardiac arrest with resuscitation, or hospitalization for unstable angina after acute coronary syndromes (ACS). **(Left)** Short-term cumulative incidence of events according to tertiles of triglycerides (TGs) at initial random assignment in the atorvastatin group of the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) trial. Time 0 corresponds to a mean of 63 h after index ACS (range: 24 to 96 h); $p = 0.03$ for trend across tertiles. **(Right)** Long-term cumulative incidence of events according to quintile of TGs at initial random assignment in the dal-OUTCOMES trial. Time 0 corresponds to a median of 6 weeks after index ACS (range: 4 to 12 weeks); $p < 0.001$ for trend across quintiles. Reproduced with permission from Schwartz et al. (38).

ROLE OF TG-LOWERING DRUGS ON CARDIOVASCULAR OUTCOMES BEYOND OPTIMAL LDL-C REDUCTION

Fibrates, niacin, and omega-3 fatty acids (OM3FA) are 3 major classes of lipid-altering agents currently available to treat elevated TG and/or low HDL-C levels in the hope of achieving adjunctive ASCVD event reduction by mitigating increased residual risk. **Table 1** presents the current evidence for the results with these agents in monotherapy trials and in a few combination therapy trials with statins (40). These results reaffirm the view that currently, statins provide the most robust evidence-based data for ASCVD event reduction as monotherapy and are the drug class of choice in primary and secondary prevention (3-5).

In monotherapy trials of patients with baseline TG levels ≥2 mmol/l (≥177 mg/dl), several clinical trials have reported significant benefits in cardiovascular event reductions (7,8,17). In the 5-year VA-HIT (Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial) study of 2,531 men with established CHD conducted before widespread use of statins, treatment with gemfibrozil versus placebo was particularly effective in patients with T2DM (n = 627). It reduced the primary endpoint of death or nonfatal myocardial infarction by 32% ($p = 0.004$), mortality by 41% ($p = 0.02$), and stroke by 40% ($p = 0.046$); however, the benefits were not attributable to changes in HDL-C or TG levels (40), and the diabetes subgroup was small, suggesting that the results might be less reliable. In the ACCORD-Lipid trial, the addition of fenofibrate to simvastatin 40 mg in the overall cohort with a median baseline TG level of 162 mg/dl yielded no significant benefit (36). However, a subgroup of 941 subjects with baseline TG and HDL-C levels in the highest tertile (≥204 mg/dl) and the lowest tertile (≤34 mg/dl),

TABLE 1 Cardiovascular Outcome Trials With Therapies for TG Lowering

	Publication Date	Population	Statin Use	Baseline LDL-C (mg/dl)*
Omega-3 fatty acid mixture studies				
GISSI-P	1999	11,324 pts recent MI (≤3 months)	Cholesterol-lowering: BL = 5% EOS = 46%	137
GISSI-HF	2008	6,975 pts chronic HF (NYHA functional class II–IV)	22.3%-23.0%	Not provided TC = 188
OMEGA	2010	3,851 pts recent MI (≤2 weeks)	94%-95%	Not provided EOS = 95
Alpha-Omega-3 fatty acid	2010	4,837 pts prior MI (median 3.7 yrs)	BL lipid-lowering = 85%-87%	99-102
SU.FOL.OM3	2010	2,501 pts recent CVD event (median: 101 days)	BL lipid-lowering = 83%-87%	101-104
ORIGIN	2012	12,536 pts dysglycemia + prior or high-risk CVD	53%-54%	112
Risk & Prevention	2013	12,513 pts High-risk CVD	41%	132
Pure EPA study				
JELIS	2007	18,645 pts hypercholesterolemic	100%	182
Fibrate studies				
HHS	1987	4,081 pts dyslipidemia + primary prevention	0%	188-189
VA-HIT	1999	2,531 pts prior CHD + HDL-C ≤40 mg/dl	0%	111
BIP	2000	3,090 pts prior MI or stable angina	0%	148-149
FIELD	2005	9,795 pts T2DM	BL = 0% EOS: placebo = 16% fenofibrate = 8%	119
ACCORD- Lipid	2010	5,518 pts T2DM + high CV risk	100%	101
Niacin studies				
AIM-HIGH	2011	3,414 pts prior CVD	100%	74
HPS2-THRIVE	2014	25,673 pts prior vascular disease	100%	63

*Mean or median values are presented. Where available, medians are preferentially presented. †**Bold values** approached/achieved statistical significance. Reproduced with permission from Bhatt et al (40).

ACCORD = Action to Control Cardiovascular Risk in Diabetes; AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes; ALA = alpha-linolenic acid; Alpha-Omega = Study of Omega-3 Fatty Acids and Coronary Mortality; BIP = Bezafibrate Infarction Prevention; BL = baseline; EOS = end of study; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; ER = extended release; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; GISSI-HF = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Heart Failure; GISSI-P = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Prevenzione; HDL-C = high-density lipoprotein cholesterol; HF = heart failure; HHS = Helsinki Heart Study; HPS2-THRIVE = Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events; HR = hazard ratio; JELIS = Japan EPA Lipid Intervention Study; MACE = major adverse cardiac events; MI = myocardial infarction; NYHA = New York Heart Association; OMEGA = Effect of Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death After Myocardial Infarction; OR = odds ratio; ORIGIN = Outcome Reduction with an Initial Glargine Intervention; pts = patients; RRR = relative risk reduction; SCD = sudden cardiac death; SU.FOL.OM3 = Supplémentation en Folates et Omega-3; T2DM = type 2 diabetes mellitus; TG = triglyceride; VA-HIT = Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial.

respectively, exhibited a 31% reduction in major ASCVD events but of borderline significance (p = 0.06). Clearly, additional studies in patients selected for hypertriglyceridemia and optimally treated with statins are needed. One such large, prospective trial (PROMINENT [Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Diabetic Patients]) with a new fibrate, pemafibrate (NCT03071692), is underway, although the results will not be available for several years. Initial short-term results of pemafibrate on TG levels and other lipids seem promising (41).

With regard to niacin added to statins, both the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) and HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) trials showed no additional clinical benefits overall in high-risk patients undergoing intensive statin treatment (32,33), despite favorable effects on both TG and HDL-C levels. However, a small subgroup analysis (n = 439) of combined atherogenic dyslipidemia (baseline TG level ≥200 mg/dl and HDL-C

TABLE 1 Continued

Baseline TG (mg/dl)*	Interventions	Duration (yrs)	Primary Endpoint	Outcomes: HR or OR (CI) or RRR (p Value)†
162	850 mg EPA + DHA vs. vitamin E vs. n-3 + vitamin E vs. placebo	3.5	Death or nonfatal MI or nonfatal stroke	**HR: 0.85 (0.74–0.98)** [4-way analysis]
126	850 mg EPA + DHA vs. placebo	3.9	Co-primary of death, and death or CV hospitalization	Death **HR: 0.91 (0.833–0.998)** Death or CV hospitalization **HR: 0.92 (0.849–0.999)**
Not provided EOS = 121 vs. 127	840 mg EPA + DHA vs. placebo	1	SCD	OR: 0.95 (0.56–1.60)
144–150	400 mg EPA + DHA vs. placebo and ALA (2 g) combined	3.3	Expanded MACE	HR: 1.01 (0.87–1.17)
97–115	600-mg EPA + DHA vs. placebo and vitamin B	4.7	MACE	HR: 1.08 (0.79–1.47)
140–142	840 mg EPA + DHA vs. placebo	6.2	CV death	HR: 0.98 (0.87–1.10)
150	850 mg EPA + DHA vs. placebo	5	CV death or CV hospitalization	HR: 0.97 (0.88–1.08)
151	1,800 mg EPA + statin vs. statin	4.6	Expanded MACE	**HR: 0.81 (0.69–0.95)**
175–177	1,200 mg gemfibrozil vs. placebo	5	Cardiac death, or fatal or nonfatal MI	**RRR: –34% (p < 0.02)**
160	1,200 mg gemfibrozil vs. placebo	5.1	CHD death or nonfatal MI	**RRR: –22% (p = 0.006)**
145	400 mg of bezafibrate vs. placebo	6.2	Sudden death or fatal or nonfatal MI	RRR: –9.4% (p = 0.26)
153–154	200 mg fenofibrate vs. placebo	5	CHD death or nonfatal MI	HR: 0.89 (0.75–1.05)
162	160 mg fenofibrate vs. placebo	4.7	MACE	HR: 0.92 (0.79–1.08)
162–164	1,500–2,000 mg ER niacin vs. placebo	3	Expanded MACE	HR: 1.02 (0.87–1.21)
108	2,000 mg ER niacin + laropiprant vs. placebo	3.9	Expanded MACE	HR: 0.96 (0.90–1.03)

level <32 mg/dl) revealed a significant 36% decrease in the expanded major adverse cardiac events (p = 0.03) (42). Moreover, in many clinical trials, niacin monotherapy or with low-dose statins reduces atherosclerotic plaque and recurrent clinical events (43), although data with high-intensity statins are lacking.

A variety of novel TG-lowering agents are being developed such as those based on an antiviral vector approach for lipoprotein lipase inhibition (22), antisense oligonucleotide approaches for apo CIII inhibition (25,26), ANGLPTL3 (28), ANGPTL4 antibody (29), and diacylglycerol acyltransferase inhibitors (7,8). However, it remains to be seen whether any of these agents will reach clinical trials for the typical range of high TG level (200 to 499 mg/dl).

In view of the disappointing results with fibrates and niacin when co-administered in statin-treated patients, there is considerable interest in OM3FA (eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA], or EPA alone) when added to high-potency statin therapy. These agents have been associated with significant reductions in both TG and non-HDL-C levels during short-term Phase III studies (44,45). There is evidence for a modest increase in LDL-C with DHA but not with EPA (46). However, most primary and secondary intervention trials (**Table 1**), or several meta-analyses, with OM3FA thus far have yielded inconsistent results in CVD outcomes (40,44,45,47–49). This scenario could be partly due to use of low-dose OM3FA, which is insufficient to effectively lower TG levels. Only 1 trial thus far, the JELIS (Japan EPA Lipid Intervention Study), was conducted (albeit with an open-label design) with a combination of low-dose EPA 1.8 g with a low-dose statin (pravastatin 10 mg or simvastatin 5 mg) (50). There was a 19% reduction in ASCVD events (p = 0.011). The median baseline TG level in the JELIS trial was 1.7 mmol/l (~150 mg/dl), and the outcomes were unrelated to the LDL-C reduction or the modest TG reduction, raising the

possibility of favorable nonlipid-mediated outcomes. However, in a subsequent analysis (51), those with higher TG levels (≥150 mg/dl) and low HDL-C levels (<40 mg/dl) exhibited the highest risk of coronary events and a 53% reduction in events (HR: 0.47; 95% CI: 0.23 to 0.98; p = 0.043).

INFLAMMATION AND POTENTIAL RELEVANCE OF PLEIOTROPIC EFFECTS OF TG-LOWERING AGENTS

It is well recognized that atherosclerosis has an inflammatory basis (52,53). There is very likely a dynamic interplay between genetic and major cardiovascular risk factors, including T2DM, hyperlipidemia, and smoking, acting in concert to initiate and perpetuate inflammatory pathways. In particular, several signaling pathways initiate inflammation via chemokines from the vessel wall, including activated myeloid cells and visceral adipocytes. In addition, inflammasomes such as nucleotide-binding domain-like receptor protein 3 activate interleukin (IL)-1β, leading to generation of several cytokines, including IL-6, tissue necrosis factor-α, and C-reactive protein (CRP) (52,54).

POTENTIAL ROLE OF OM3FA IN ASCVD EVENT REDUCTION

Statins are known to inhibit inflammatory pathways and reduce biomarkers such as IL-6 and CRP (52,54). Fibrates may exert anti-inflammatory, immunomodulatory, and antithrombotic effects via peroxisome proliferator-activated receptor alpha gene activation; they also reduce IL-6, CRP, and fibrinogen levels in patients with ASCVD (55). The effects of OM3FA on inflammatory pathways have been of considerable recent interest (56,57). In short-term trials, EPA 4 g in patients with a median TG level of 680 mg/dl led to a 33% reduction in TG levels (58) and a 22% reduction in TG levels among statin-treated patients with a median baseline TG level of 259 mg/dl (59). This outcome was accompanied by reductions in the inflammatory biomarkers CRP, lipoprotein-associated phospholipase A2, and apo CIII. In mice and humans, EPA has also been shown to increase adiponectin, an insulin-sensitizing adipokine (60,61). A recent provocative study revealed that, in pregnant women in their third trimester, oral supplementation with EPA or DHA resulted in a significant reduction in the risk of asthma or wheezing in infants up to 5 years of age (62), particularly when the baseline maternal EPA and DHA levels were low (risk reduction: 54%; p = 0.011). Such observations further support the potential protective effects of OM3FA in resolving inflammation, likely via leukotriene-mediated effects.

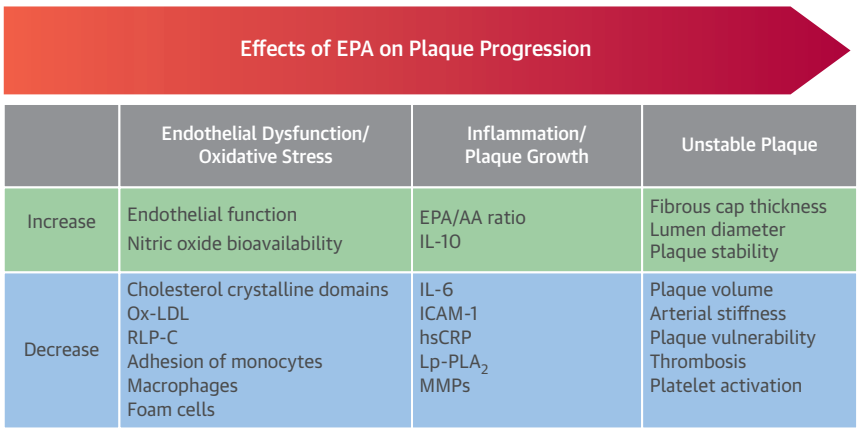
Of additional interest are the results from a recently published trial with canakinumab, a monoclonal antibody targeting IL-1β, on ASCVD outcomes in 10,006 stable patients after a myocardial infarction and with baseline CRP levels ≥2.0 mg/l (63). Most subjects were treated with statins, with a median LDL-C level of 82 mg/dl at baseline. Treatment with canakinumab resulted in a significant reduction in the composite primary outcome of cardiovascular death, nonfatal myocardial infarction, or stroke (HR: 0.85; 95% CI: 0.74 to 0.98; p = 0.02). These results support mounting evidence of an anti-inflammatory hypothesis and treatment paradigm to reduce ASCVD events beyond statin use (54).

MOLECULAR BASIS OF ACTION OF OM3FA

Recent research has elucidated the cardiovascular actions of OM3FA (56,64). OM3FA have an essential role in various tissues, influencing cellular membrane width and the formation and stability of lipid rafts. They also serve as precursors for bioactive lipid mediators that regulate inflammation, including eicosanoids, prostaglandins, leukotrienes, protectins, and resolvins (57). With the incorporation of EPA into cellular membranes associated with the atherosclerotic plaque, it interferes with lipid oxidation and various signal transduction pathways linked to inflammation, endothelial dysfunction, and plaque instability. In particular, the lipophilic structure and space dimensions allow EPA to insert efficiently into lipoprotein particles and cell membranes where it scavenges free radicals (64). DHA is also a long-chain OM3FA with various functions in nervous tissue and retinal cells (65). Due to differences in their structure and molecular conformations, EPA and DHA associate with distinct regions of biological membranes and differentially modulate membrane structure-function relationships (64).

EPA also differs from DHA in its duration of antioxidant activity and its effects on cell membrane lipid structure and dynamics. The antioxidant effects of EPA are attributed to its ability to quench reactive oxygen species associated with cellular membranes and lipoproteins. The effects of EPA could not be reproduced with vitamin E or other TG-lowering agents, under normal or hyperglycemic conditions (56,66). The antioxidant activity of EPA was not observed with other TG-lowering agents or DHA in lipoprotein particles. Unlike EPA, DHA has been

FIGURE 3 Effects of EPA on Atherogenesis



Multiple salutary effects of eicosapentaenoic acid (EPA) on endothelial dysfunction, oxidative stress, inflammation, and plaque stability. AA = arachidonic acid; hsCRP = high-sensitivity C-reactive protein; ICAM = intercellular adhesion molecule; IL = interleukin; Lp-PLA_2 = lipoprotein-associated phospholipase A2; MMPs = matrix metalloproteinases; Ox-LDL = oxidized low-density lipoprotein; RLP-C = remnant-like lipoprotein particle cholesterol.

shown to undergo rapid conformational changes, whereas EPA assumes a stable, extended orientation (64). Along with oxidized LDL, cholesterol crystals are also a primary activator of nucleotide-binding domain-like receptor protein 3 inflammasomes. The antioxidant effects of EPA in highly atherogenic LDL subfractions (small dense LDL) from human subjects were enhanced in combination with atorvastatin under in vitro conditions (66). This unexpected finding indicates a shared location in which intermolecular interactions further stabilize unpaired lipid free radicals and thereby reduce oxidative damage. **Figure 3** summarizes the various biologic effects of EPA on the steps of atherogenesis.

ONGOING CLINICAL TRIALS WITH N-3 FATTY ACIDS ADDED TO STATINS

A recent meta-analysis of 10 RCTs (67,68) evaluated trials using very different formulations of OM3FA (67). A number of the trials used some form of unregulated supplements, whereas others used a form of mixed OM3FA that contains ethyl esters of EPA (465 mg) and DHA (375 mg). As noted earlier, JELIS used a pure EPA prescription product (50). The heterogeneous sources of OM3FA used in these studies make interpretation of the results challenging. Fish oil supplements reportedly have deficiencies in both the quality and quantity of OM3FA (69). Supplements have been shown to have less OM3FA than claimed and to contain substantial amounts of oxidized lipids and significant amounts of undesirable saturated fats. Finally, most of the studies in this meta-analysis used low-dose OM3FA (<1 g) supplements that are inadequate for effective and sustained TG lowering. By contrast, some ongoing prospective RCTs are using prescription formulations of OM3FAs at doses (3 to 4 g/day) that do lower TG levels effectively.

Several large RCTs are currently evaluating the addition of OM3FA to therapy for statin-treated patients (**Table 2**). Two of these have a more rigorous design with the important trial inclusion of LDL-C level <100 mg/dl at baseline: the REDUCE- IT trial (Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention; NCT01492361) and the STRENGTH trial (Statin Residual Risk Reduction With EpaNova in High Cardiovascular Risk; NCT02104817).

The design of the REDUCE-IT trial has been published (40). Briefly, it is a Phase IIIb RCT of icosapent ethyl (EPA), a highly purified ethyl ester of EPA, versus placebo. The main objective is to evaluate whether treatment with EPA reduces ASCVD events in statin-treated patients with high baseline TG levels (200 to 499 mg/dl) and elevated cardiovascular risk for subsequent clinical events, and whose LDL-C levels with statins are between 40 and 100 mg/dl. This trial has enrolled ~8,000 men and women with established ASCVD or with high risk T2DM. The trial results are expected in late 2018.

TABLE 2 Ongoing RCTs With Omega-3 Fatty Acids and CV

Trial Location	N Age, yrs	Design	Formulation, Dose	Duration, yrs	Expected Completion Date	Comment
REDUCE-IT United States	~8,000 ≥45	Secondary prevention if CVD; primary if diabetes with risk factors	EPA, 4 g	5.0	2018	LDL-C <100 mg/dl, on statin TG 150–499 mg/dl
STRENGTH United States	13,086 18–99 (>40 if diabetes)	Secondary prevention if CVD; primary if diabetes with risk factors	EPA + DHA Carboxylic acids, 4 g	5.0	2020	LDL-C <100 mg/dl, on statin TG 180–499 mg/dl HDL-C <42 mg/dl in men, <47 mg/dl in women
RESPECT-EPA Japan	3,900 20–79	Stable CAD	EPA 1.8 g	5.0	2022	Statin treated open-label
OMEMI Norway	1,400 70–82	Post-MI, stable	EPA + DHA 1.8 g	2-4	2020	Statin treated
VITAL United States	25,854 Men ≥50 Women ≥55	Primary prevention 2 × 2 factorial with vitamin D	EPA + DHA 1 g	5.0	2018	39% on statin
ASCEND United Kingdom	15,480 ≥40	Primary prevention 2 × 2 factorial with aspirin	EPA + DHA 1 g	7 .0	2018	All patients with diabetes; 75% on statin Pragmatic design, sampling by mail via PCPs

ASCEND = A Study of Cardiovascular Events in Diabetes; CAD = coronary artery disease; OMEMI = Omega-3 Fatty Acids in Elderly Patients With Myocardial Infarction; PCP = primary care physician; REDUCE-IT = Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial; RESPECT-EPA = Randomized Trial for Evaluation in Secondary Prevention Efficacy and Combination Therapy–Statin and EPA; STRENGTH = Statin Residual Risk Reduction With EpaNova in High Cardiovascular Risk; VITAL = Vitamin D and Omega A3 trial; other abbreviations as in Table 1.

Unlike JELIS, which enrolled a considerable proportion of patients with normal baseline TG levels and used a relatively low dose of EPA (50), REDUCE-IT is the first RCT to employ a more robust dose (4 g of EPA in high-risk patients) with high baseline TG levels. Several other primary prevention trials, including VITAL (Vitamin D and Omega A3) and ASCEND (A Study of Cardiovascular Events in Diabetes) (Table 2), are using doses of OM3FA ranging from 1 to 1.8 g, which may be less effective therapeutically because most of the previous trials using such low doses have not shown positive results (40,67) (Table 1). Moreover, in the VITAL trial, only 39% of patients were taking statins at baseline, whereas 75% of subjects reported taking statins at randomization in ASCEND.

In another Phase IIIb RCT (STRENGTH), a free fatty acid formulation of EPA + DHA is being tested against placebo in a similar study design as the REDUCE-IT trial. The exception is that in STRENGTH, an additional requirement is an HDL-C level <40 mg/dl at baseline in addition to elevated TG levels similar to the REDUCE-IT trial. In short-term dose-ranging studies in patients with TG levels of 200 to 499 mg/dl, or in subjects with TG levels ≥500 mg/dl, this formulation resulted in a significant 21% and 31% decrease in TG levels, respectively, and significant reductions in apo CIII and lipoprotein-associated phospholipase A2 but no significant change in CRP levels (70,71).

With the recent availability of proprotein convertase subtilisin/kexin type 9 inhibitors for intensive LDL-C reduction beyond statins (3,72,73), it is worth considering the potential impact of OM3FA supplementation on further reducing residual risk. Specifically, the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial showed that in stable ASCVD patients, most of whom were receiving high-potency statins, there was a modest, incremental 15% to 20% overall ASCVD risk reduction with the addition of evolocumab (72) during a median follow-up of 26 months; no significant reductions in cardiac death or all-cause mortality were observed, however. If TG reduction improves CVD risk beyond LDL-C, the potential added benefit of OM3FA may be considerable, especially in patients with diabetes at high ASCVD residual-risk burden and frequently high TG levels in addition to elevated LDL-C.

RETURNING TO THE CASE

The present case patient is at very high risk of recurrent ASCVD owing to a background of T2DM, hypertension, chronic kidney disease, and premature ASCVD. In considering therapeutic strategies to reduce his residual risk, recent data from the IMPROVE-IT (ezetimibe) and FOURIER and ODYSSEY

Outcomes (proprotein convertase subtilisin/kexin type 9 inhibitor) trials have shown further reductions in ASCVD of between 6% and 15% to 20%, respectively, after co-administration with statins. However, these LDL-lowering agents do not appreciably reduce TG levels. Although fibrates reduce TG levels, they were associated with inconclusive effects when added to statins in the ACCORD-Lipid trial (36). In patients with TG levels of 200 to 499 mg/dl, OM3FA have been shown to improve dyslipidemia and inflammatory biomarkers. With the recent data on the potential pleotropic effects of OM3FA on plaque stabilization, there is a resurgence of interest in their potential favorable effects on ASCVD events. Two such trials in statin-treated patients are nearing completion and will likely inform clinical practice for this treatment combination in subjects with mixed dyslipidemia.

CONCLUSIONS

There is a persistent residual risk of ASCVD even after intensive statin therapy has been initiated and as defined by current guidelines. The prevalence of atherogenic dyslipidemia is increasing with the global epidemics of obesity, metabolic syndrome, and T2DM. Genetic studies have provided strong scientific evidence that elevated TG levels are associated with incident ASCVD events. Both genetic and clinical trials have thus far failed to conclusively establish HDL-C level as a significant contributor to ASCVD events, nor have interventions directed at raising low levels of baseline HDL-C shown convincing evidence of cardiovascular event reduction, even when LDL-C is "optimally" controlled with statins. Fibrates are effective in reducing elevated TG levels; however, to date, the evidence for their role in reducing residual risk when combined with statins remains uncertain. OM3FA are also effective agents in lowering elevated TG levels. In addition, they seem to exhibit pleiotropic effects in reducing plaque instability and proinflammatory mediators that underlie and potentiate atherogenesis. At the molecular level, there is accumulating evidence that EPA, compared with DHA, elicits more favorable effects on arterial inflammation. Currently, a long-term clinical trial testing high-dose (4 g) EPA in statin-treated patients with ASCVD or high-risk patients with diabetes is nearing completion, and another trial with EPA + DHA will likely conclude in 2019 to 2020.

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ADDRESS FOR CORRESPONDENCE: Dr. Om P. Ganda, Joslin Diabetes Center, Harvard Medical School, 1 Joslin Place, Boston, Massachusetts 02215. E-mail: om.ganda@joslin.harvard.edu.

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