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REVIEW TOPIC OF THE WEEK

Unmet Need for Adjunctive Dyslipidemia Therapy in Hypertriglyceridemia Management

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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;■:■–■) © 2018 by the American College of Cardiology Foundation.

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.

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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

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

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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