The Editor's Roundtable: Hypertriglyceridemia

Vincent E. Friedewald, MD[a,*], Christie M. Ballantyne, MD[b], Harold E. Bays, MD[c], and Peter H. Jones, MD[d]

Disclosures

Dr. Friedewald has no conflicts to disclose. Dr Ballantyne has received research grants and honoraria from Amarin Pharma, Inc. and has also received research grants and served as a consultant and speaker for numerous other pharmaceutical companies. Dr. Bays has received research grants and served as an adviser to Amarin Pharma Inc. and has also received research grants and served as a consultant and speaker for numerous other pharmaceutical companies. Dr. Jones is a consultant for Atherotech, Birmingham, Alabama; Merck, Whitehouse Station, New Jersey; Amarin; and Amgen, Thousand Oaks, California and is the Chief Science Officer for the National Lipid Association.

Introduction

Hypertriglyceridemia is defined as a fasting serum triglyceride (TG) level of ≥150 mg/dl.[1] Serum TG elevations are designated as

Borderline: 150 to 199 mg/dl,
High: 200 to 499 mg/dl,
Very high: ≥500 mg/dl.

Currently, 31% of the population in the United States have TGs >150 mg/dl, unchanged for the past 2 decades. Mexican Americans have the highest rates of hypertriglyceridemia, with 9% of Mexican American men aged 50 to 59 years having very high TGs compared with 1% to 2% of the overall population with very high TGs. African-Americans have the lowest prevalence (15.6%) of hypertriglyceridemia.

Although hypertriglyceridemia affects so many persons, its clinical significance is unclear—except for the long-established relation between very high TGs and pancreatitis. Whether elevated TGs are a direct cause or only a marker for atherosclerosis has been a topic of debate for many years. This question and other issues, including evaluation and best treatment of patients with elevated TGs, are addressed in this Editor's Roundtable.

Dr. Friedewald: What do we know about the relation between serum triglycerides (TGs) and disease?

Dr. Jones: TGs are a good marker of at least one serious disease: acute pancreatitis. Clinical pancreatitis can occur with serum TGs levels of >500 to 1,000 mg/dl.

At lower serum levels, TGs are the beginning of a cascade of metabolism into low-density lipoprotein cholesterol (LDL-C) particles. The liver produces very low-density lipoproteins (VLDLs), which are progressively metabolized, with removal of TGs, to cholesterol-enriched LDL particles. In the postprandialstate, all ingested and absorbed TGs are transported in TG-rich lipoproteins, termed chylomicrons.

An increase in TG-rich lipoproteins also modifies other lipoproteins. For example, LDL particles and high-density lipoprotein cholesterol (HDL-C) particles become smaller in size when TG particles are poorly cleared and metabolized. Thus, there is an intimate relationship between elevated serum TGs and other lipoproteins.

We do not understand the mechanism underlying the well-established clinical association between elevated TGs and the body's greater physiological propensity toward insulin resistance. For example, an important question is, which comes first: insulin resistance or abnormal TG metabolism? This is important in managing patients with the metabolic syndrome.

Dr. Friedewald: What is the significance of TG particle *size* versus TG particle *number*?

Dr. Jones: Particle size is an inverse surrogate measure for particle number: smaller particle size means greater particle number. I do not believe that particle size is clinically important. After controlling for particle number, size drops out as a cardiovascular (CV) risk predictor. The *number* of atherogenic particles is the primary determinant of CV risk.

Dr. Bays: Many experts believe that smaller and denser LDL particles are more atherogenic. Increased numbers of smaller and denser LDL particles often accompanies other underlying atherogenic risk factors (e.g., pathogenic adipose tissue or adiposopathy, insulin resistance with or without hyperglycemia, and high TG levels). There is a fundamental difference, however, between ordering a test for lipoprotein particle size for the purposes of assessing CV disease risk, versus assessing the effectiveness of a therapeutic intervention. I do not believe that particle size has relevance in measuring efficacy of lipid management. Therapeutically, other lipid parameters take precedence, such as LDL-C and non−HDL-C levels, as well as atherogenic particle number, which is clinically assessed by measuring apolipoprotein B (apo B).

Dr. Friedewald: How do you explain TGs to patients?

Dr. Ballantyne: TGs are composed of glycerol and 3 fatty acids—*tri*-glycerides. Their function is to transport energy. When discussing with patients, I explain TGs in

[a]Associate Editor, *The American Journal of Cardiology*, and Clinical Professor of Medicine, University of Texas Health Science Center, Houston, Texas; [b]Professor of Medicine and Director, Center for Cardiovascular Disease Prevention, Houston Methodist DeBakey Heart and Vascular Center, Baylor College of Medicine, Houston, Texas; [c]Medical Director, Louisville Metabolic and Atherosclerosis Research Center, Louisville, Kentucky; and [d]Associate Professor of Medicine, Houston Methodist DeBakey Heart and Vascular Center, Baylor College of Medicine, Houston, Texas. Manuscript received July 29, 2013; accepted July 30, 2013.

This article is supported by a grant from Amarin Pharma, Inc., Mystic, Connecticut.

This discussion took place on July 5, 2013, at the Texas Medical Center, Houston, Texas.

See page 1140 for disclosure information.

*Corresponding author: Tel: (512) 417-5379; fax: (512) 264-7034.
E-mail address: vef@argus1.com (V.E. Friedewald).

Am J Cardiol 2013;112:1133−1141
0002-9149/13/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2013.07.033

relation to body fat, which they easily understand. I tell them that fat wraps around the liver and pancreas, which is important because the liver makes TG particles and the pancreas handles glucose and insulin. That is how fat relates to the metabolic syndrome. Elevated TGs are important in disorders of energy metabolism, particularly obesity and diabetes mellitus (DM).

Dr. Bays: TG levels are elevated by both increased production and decreased clearance. Obesity is, in my opinion, a disease because increased body fat causes dysfunctional or "sick fat" *(adiposopathy)*, which results in pathologic immunopathies and endocrinopathies, with 1 clinical manifestation being impaired energy storage.[2,3] TGs are fats in the bloodstream, carried by lipoproteins. If TG storage in adipose tissue is impaired, then TGs may build up in the blood, resulting in hypertriglyceridemia. When TG levels are *very* high, there is increased risk of pancreatitis. But even lower TG levels suggest the presence of TG-rich lipoproteins, which, in addition to LDL-C, are atherogenic. Thus, both serum TGs and LDL-C must be measured when assessing CV disease risk.

Dr. Friedewald: At what level do TGs increase the risk for CV disease?

Dr. Bays: In general, TG levels from 200 to 500 mg/dl are thought to potentially increase CV risk. The challenge is that at this time, there are no *prospective* trial results proving that reducing TGs prevents atherosclerosis or improves outcomes. There has been no trial requiring hypertriglyceridemia as part of entry criteria and specifically assessing whether a TG-lowering intervention (compared to placebo) reduced CV events. All we have, to date, are *post-hoc* subset analyses of CV outcome studies that did not require elevated TG levels at study entry.

Dr. Friedewald: How does hypertriglyceridemia cause pancreatitis?

Dr. Jones: As serum TGs rise—especially with serum levels >1,000 mg/dl—TGs are no longer derived solely from the liver (e.g., VLDLs), but are also composed of postprandial TGs in the form of chylomicrons. High levels of postprandial serum chylomicrons and VLDLs are poorly cleared from the bloodstream, causing abnormal blood viscosity. This gives a milky appearance to the plasma. Increased blood viscosity due to chylomicrons probably causes micro-infarctions in the pancreas, and along with digestive pancreatic enzymes, results in auto-digestion of the pancreas, which can be self-perpetuating and serious, even leading to multi-organ failure.

Dr. Friedewald: You said the function of TGs was to transport energy. Is there an entity in which TGs are too low, causing low energy states? Do high levels of TGs cause symptoms?

Dr. Jones: TGs are never abnormally *low*. Low or normal TG levels do not directly contribute to symptoms due to loss of energy, such as fatigue. *Extremely* high TG levels (>20,000 mg/dl) might cause mental changes such as confusion. Patients with high TGs are asymptomatic unless they develop pancreatitis.

Dr. Bays: Primary genetic disorders, often coupled with secondary causes, most often account for the clinical finding of very high TG levels. Examples of secondary causes of hypertriglyceridemia include positive caloric balance in patients with adiposopathy, untreated hypothyroidism, uncontrolled DM, nephrotic syndrome, certain medications, and acute alcohol consumption.[4,5]

Dr. Friedewald: How do you assess patients with high TGs?

Dr. Bays: First, you take a family history. Patients with TGs >500 mg/dl usually have a primary genetic abnormality. In taking the past medical history, patients should be carefully assessed for potential secondary causes of high TGs.

Dr. Ballantyne: The workup is simple: medication and family history, good physical examination, and a rule-out of secondary causes. Liver function tests should be performed because liver disease sometimes causes high serum cholesterol and TGs, and urinalysis and kidney function tests for nephrotic syndrome.

One more comment about symptoms. Some patients have chylomicronemia syndrome, causing headaches and eruptive xanthomas—manifest as a raised rash, like pimples. Xanthomatosis points to the notion that TG-rich lipoproteins are pro-inflammatory, and inflammation is another component of pancreatitis.

Dr. Friedewald: What does a biopsy of an eruptive xanthoma show?

Dr. Ballantyne: A biopsy shows acute inflammation with leukocytes, monocytes, and macrophages.

Dr. Friedewald: Are markers of inflammation, such as elevated serum C-reactive protein (CRP), seen in patients with elevated TGs?

Dr. Ballantyne: I suspect that CRP is elevated in these patients, but we do not usually measure it.

Dr. Friedewald: Does lowering the TG level reduce the risk of acute pancreatitis?

Dr. Ballantyne: The frequency of pancreatitis appears to be drastically lowered by treating high TGs, but this has not been studied in a controlled trial.

Dr. Bays: Conduct of such a trial would be problematic because such a trial would require enrolling patients with very high TG levels with prior histories of pancreatitis (a serious, sometimes fatal illness), washing them of TG-lowering therapy, and then randomizing them to a TG-lowering intervention or placebo. The outcome primary measures would likely be the number of bouts of pancreatitis in the intervention group versus the placebo group, with secondary endpoints probably including comparisons of the onset of hemorrhagic pancreatitis, permanent diabetes mellitus (DM), and death. Few, if any, investigators would participate in such a study.

Dr. Friedewald: In addition to skin and the pancreas, what other organs are directly affected by high TGs?

Dr. Jones: Fat also infiltrates the liver and skeletal muscle. Cardiac function is probably reduced due to increased myocyte TGs. The pancreas is most affected due to blood hyperviscosity and the autodigestive capacity of pancreatic enzymes, which are not present in other organs.

Dr. Friedewald: Are elevated TGs a factor in heart failure?

Dr. Ballantyne: Defects in fatty acid metabolism are a factor in heart failure, because fatty acids are energy substrates. Inherited defects in fatty acid metabolism can cause cardiomyopathy.

Dr. Jones: Some patients with hypertriglyceridemia and insulin resistance appear to have abnormal ventricular diastolic relaxation, so they may be more prone to diastolic heart failure. Thus, losing weight, lowering TGs, and increasing insulin sensitivity will probably improve left ventricular diastolic dysfunction in patients with underlying heart failure.

Dr. Friedewald: How do elevated TGs relate to atherogenesis?

Dr. Bays: In environmentally and genetically susceptible individuals, positive caloric balance may lead to adipocyte hypertrophy and accumulation of adipose tissue in areas other than subcutaneous adipose tissue depots. Increased visceral fat accompanies adiposopathy. Less recognized is that adiposopathy may increase the accumulation of perivascular and pericardial adipose tissue, which may result in "outside-to-in" inflammatory signaling that promotes atherosclerotic processes within the arterial subendothelium. I believe this is another way in which adiposopathy, as often reflected by elevated TG levels, and may contribute to atherosclerosis.[2]

Dr. Ballantyne: We generally focus on intra-abdominal fat, but ectopic fat in skeletal muscle is also important. Just look at a rib-eye steak. This has been poorly studied so far, but skeletal muscle fat may be a prime driver of insulin resistance and abnormal glucose metabolism in DM.

Dr. Jones: Insulin resistance increases with accumulating intramyocyte and perimyocyte fat. Ceramide and other factors also may play a role in decreasing sensitivity to insulin and glucose uptake in muscle. In addition, gluconeogenesis is not appropriately suppressed by insulin when there is increased fat deposition within the liver.

Dr. Bays: This is another example of the adverse consequences of adiposopathy, wherein impaired storage of energy in subcutaneous adipose tissue increases fat deposition in other organs, such as muscle and liver. Impaired energy storage in adipose tissue can increase free fatty acid delivery to the liver, which in turn increases TG secretion in the form of VLDLs, accounting for fasting hypertriglyceridemia.[6,7]

Dr. Friedewald: Are TG-enriched lipoproteins atherogenic?

Dr. Ballantyne: This is an exciting area of research. For the past several years, the focus on causes of atherosclerosis—in addition to LDL-C—has been on low levels of high-density lipoprotein cholesterol (HDL-C). Today, however, genetic studies are pointing us back to TG-receptor proteins as therapeutic targets, away from HDL-C. The gene with the most impact on HDL-C levels is endothelial lipase, which has no association with coronary atherosclerosis. The genes that are associated with low HDL-C levels and coronary artery disease (CAD) are all also associated with serum TGs and LDL-C. Postprandial lipemia reaches higher levels and lasts longer in persons with DM, particularly in patients with DM and CAD.

Dr. Jones: Postprandial lipemia is a powerful predictor of CAD.

Dr. Ballantyne: Postprandial lipemia is inversely associated with serum HDL-C levels. TGs are extremely variable, and serum glucose does not predict coronary events, although hemoglobin A_{1c} is a predictor. Low HDL-C appears to be a predictor of CAD due to high serum levels of TG-rich lipoproteins in the postprandial state. I believe TG-rich lipoproteins are atherogenic. These consist of VLDL remnants, chylomicron remnants, and intermediate-density lipoproteins. The small, dense LDLs are also important. All of these are elevated in the postprandial state.

Dr. Bays: In assessing patients with hypertriglyceridemia, measuring LDL-C alone is not enough. Other potential atherogenic parameters should also be measured, including non−HDL-C, which is the total cholesterol minus HDL-C. Non−HDL-C reflects the total amount of cholesterol carried by atherogenic lipoproteins, including TG-rich lipoproteins. Other lipid parameters to consider are apo B, or atherogenic lipoprotein particle number.

Dr. Jones: Elevated TGs are markers of a very disturbed lipid system involving impaired clearance of fasting and postprandial lipoproteins. TGs are also associated with remodeling of LDL and HDL particles. TGs are directly atherogenic when they are present as remnant lipid particles.

Dr. Ballantyne: Macrophages in the arterial wall—which are monocytes in the circulation—may also be important in atherosclerotic plaque development. In the postprandial state, in the presence of high TGs, lipids appear in macrophages—foamy monocytes. They are part of the inflammatory process.

Dr. Jones: This is true in people with mild TG elevations, the so-called Type IV dyslipidemia, in patients with very low LDL-C and low total cholesterol (<150 mg/dl), but in whom the TGs are elevated in the range of 300 to 400 mg/dl. These people do not get premature CAD, probably because they have very low levels of LDL-C.

Dr. Bays: Persons with a combination of high TGs and high LDL-C are at very high risk for CAD.

Dr. Friedewald: How do you measure the TGs?

Dr. Bays: Some experts prefer postprandial measurements. Others believe that random measurements are best, because they are most convenient for patients. For routine management of hypertriglyceridemic patients, I prefer to measure fasting TGs, because TG levels are inherently variable (and thus reported as *median* in clinical trials), with fasting perhaps providing less variability and the best chance for reasonable comparative assessments from office visit to office visit. Also, the majority of clinical trials for which the efficacy of therapeutic interventions are reported are based on fasting TGs. Most lipid assessment and treatment guidelines are based on fasting TG levels.

Dr. Jones: It is, however, difficult for patients to remain fasting until their afternoon office appointments. For that reason, the American Heart Association recommendations approve non-fasting TG measurements.[1] Based on that level, you can decide what to do, because if the non-fasting TG level is in the 100 to 125 mg/dl range, no more measurements are needed. If the TG is >200 mg/dl, however, there should be a fasting measurement. We should not miss opportunities to evaluate patients for CV risk simply because they are not fasting, and some lipid measures are unaffected by meals, such as non−HDL-C.

Dr. Bays: After treatment is started, however, you do prefer fasting TGs, do you not?

Dr. Jones: Yes, although when focusing mainly on non−HDL-C, fasting is still unnecessary.

Dr. Ballantyne: The time that serum lipids should be measured depends on what you are treating. For patients

with CAD, your main concern is the response of LDL-C to statins. That measure can be non-fasting. I personally prefer fasting TG levels for another reason, however, and that is to also measure the fasting serum glucose. Detecting an elevated fasting glucose is an additional motivating factor for diet and exercise, as patients relate more strongly to DM than they do to pure lipid measures. It is surprising how many patients have DM, and they do not realize it, because physicians often do not pay serum glucose the same attention that they pay to serum lipids.

Dr. Friedewald: When interpreting elevated TGs, do you inquire about diet?

Dr. Jones: Diet comes into play in CV risk reduction, but not in interpreting lipid levels.

Dr. Friedewald: If we could perform it, what would an ambulatory 24-hour TG measurement look like?

Dr. Jones: In somebody who tends to have high postprandial lipemia because of a disturbed lipid system, it depends on what they eat. Most people, however, are in a perpetual postprandial state. With normal lipid metabolism and normal fasting TGs, no underlying insulin resistance, and after a reasonable meal, the TGs probably do not go much above 200 to 250 mg/dl during the first 4 to 6 hours after eating, and they return to normal by 8 hours. Persons with very disturbed handling of TGs due to background genetic and environmental influences have a TG level of 250 mg/dl before eating and it rises to 500 to 800 mg/dl after the meal, remaining elevated for as long as 10 hours before declining. Thus, intervals of 6 hours between meals results in constantly elevated TG levels, never returning to the "fasting" level in these persons. People rarely go as long as 10 to 12 hours between meals, so patients with abnormal TG metabolism are always well above 250 mg/dl.

Dr. Bays: Dietary diaries can be very helpful in evaluating patients with hypertriglyceridemia for compliance when a low carbohydrate is prescribed. A dietary diary helps when recommending lower glycemic index/load carbohydrate choices. Alcohol consumption also contributes to hypertriglyceridemia, so a history of alcohol consumption is important.

Dr. Friedewald: What is the next step after obtaining a random elevated TG level?

Dr. Jones: First, look at the non−HDL-C level. If it is elevated, the next step is to repeat the measure while fasting to determine the baseline TGs, as well as getting another measure of the non−HDL-C. This provides a complete look at overall CV risk as it relates to serum lipids.

Dr. Friedewald: What lifestyle changes are effective in treating patients with elevated TGs?

Dr. Jones: Of all the lipid particles that can be altered with lifestyle, TGs are the most amenable. This starts with a change in diet composition. Low glycemic index diets and reduced total fat diets are remarkable in how quickly they lower serum TGs. In some patients with TG levels of 2,000 to 3,000 mg/dl an abrupt dietary change to a high-protein, low-carbohydrate diet and no alcohol causes a 50% to 70% fall in TGs within 5 days. Thus, a change in diet can cause a huge change in TGs, and this is independent of the effect of diet on adiposity. Further weight reduction decreases the stimulus for overproduction of TGs, which improves insulin sensitivity, and this further improves clearance of TGs. In this diet, *total* alcohol cessation is essential in lowering TGs in susceptible people.

Dr. Friedewald: What is the role of physical exercise in lowering TGs?

Dr. Jones: Physical activity increases insulin sensitivity and muscle utilization of TGs. Exercise also increases activity of endothelial lipase and lipoprotein lipase, which clears both fasting and postprandial TGs. Thus, TG reduction requires a complete lifestyle change: abstaining from alcohol; reducing glycemic index, total carbohydrates and total calories; and increasing physical activity—and all these changes have to be undertaken at the same time. They are, however, incredibly effective.

Dr. Bays: Not only are these measures helpful in reducing TG levels, but they also improve other metabolic parameters often associated with elevated TG levels, such as hyperglycemia.

Dr. Ballantyne: Talking to patients about energy metabolism and fat is simple. Eat fewer carbohydrates and fats.

Dr. Jones: Simple to say, but hard to do.

Dr. Friedewald: What medications do you prescribe for elevated TGs, starting with the older drugs—niacin, fibrates, and omega-3 fatty acids?

Dr. Bays: According to prescribing information, extended-release prescription niacin is indicated for use in patients with TGs $\geq$500 mg/dl. However, although niacin definitely lowers TGs, I am unaware of any definitive clinical trial that has demonstrated its efficacy in patients exclusively enrolled in a trial with TGs $\geq$500 mg/dl.

Dr. Jones: Fibrates have been available for almost 30 years, and they have been traditionally used to treat high TGs, even in patients with TGs $>$500 mg/dl. Niacin also lowers TGs, probably through a different mechanism than fibrates. Omega-3 fatty acids, which have come into more frequent use in recent years, are also effective. When TGs are $>$500 mg/dl—and definitely are $>$1,000 mg/dl—you are not going to prescribe just 1 drug; rather, you are going to use a combination. In our clinic we usually use at least 2 drugs, and 3 drugs for patients who will take niacin.

Dr. Ballantyne: Let's not forget that statins—particularly high-efficacy statins—also lower TGs. Statins can be used as first-line therapy for TG elevations in the range of 200 to 500 mg/dl.

Dr. Jones: Whenever there is a possibility of adding a statin later, or in patients already taking statins, gemfibrozil should not be prescribed, due to the drug-drug interaction that increases the risk of rhabdomyolysis. In such cases, fenofibrate should be prescribed.

Dr. Friedewald: How effective are statins in reducing TGs?

Dr. Bays: Overall clinical trial data suggests statins reduce TG levels by 20% to 30%, while fibrates and omega-3s lower TG levels by 30% to 50%, according to different reports. An important concept in assessing metabolic outcomes is that the greatest improvements with drug intervention are among patients with the worst baseline values (e.g., blood glucose, blood pressure, TGs). When evaluated in patients with elevated TG levels, statins lower TGs to a similar degree as omega-3 fatty acids and fibrates.[7]

Dr. Friedewald: Does ezitamide have a TG-lowering effect?

Dr. Ballantyne: Ezitamide has a modest effect on TGs. As monotherapy, its effect is about 18% reduction, so it would not be sole first-line therapy.

Dr. Bays: A common misconception is that all lipid-altering drugs lower TG levels, which is untrue. For example, bile acid sequestrants (resins) may actually *increase* TGs.

Dr. Ballantyne: This brings us back to all the other medications that can elevate TGs, such as oral hormones, isoretinoic acid, protease inhibitors, and beta-blockers. A drug history is very important in treating patients with elevated TGs.

Dr. Friedewald: Is niacin effective in low doses that do not cause side effects?

Dr. Jones: No, low doses of niacin are not effective in lowering TGs. Data tell us that 1,000 mg per day, or more, is needed for the TG-lowering effect.

Dr. Friedewald: Because fibrates *raise* the LDL-C, why would you not *always* begin treatment for hypertriglyceridemia with a statin?

Dr. Jones: If the TGs are >500 mg/dl, I start the fibrate first because that will certainly lower the TGs to a reasonable range, and then maybe add the statin if I believe that the patient is at sufficient long-term risk of CV disease. When I am treating primarily hypertriglyceridemia, lifestyle changes and a fibrate suffice. For example, I would not use a statin in a 25-year-old patient with hypertriglyceridemia if the LDL-C is acceptable. If the TGs are <500 mg/dl, however, a statin could be started first, and a second drug—such as a fibrate—could be added later if needed.

Dr. Friedewald: How often do you see patients with elevated TGs and normal LDL-Cs?

Dr. Bays: As an endocrinologist, I *often* see type-2 DM patients with elevated TGs, and LDL-Cs that are not especially elevated. This can be deceiving, however, because for the same LDL-C levels, patients with type-2 DM may have higher levels of LDL particles. Thus, elevated TGs in a patient with type-2 DM may be a signal that a "normal" LDL-C is not necessarily benign. This has therapeutic implications because by definition, patients with DM are at increased risk for atherosclerotic CV disease. For this reason I gravitate more toward starting with statins in treating patients with elevated TGs. The good news is that clinical data support improved CV disease outcomes in hypertriglyceridemic patients treated with statins. I also recommend appropriate nutritional and physical interventions, which we already discussed. Sometimes, even modest increases in physical activity can have significant effects in reducing TGs.

Dr. Friedewald: What levels and types of exercise do you recommend?

Dr. Bays: This is a common question. My sense is that the best exercise for patients is *whatever they will do*. Most data suggest that the greatest benefits are derived from rigorous and regimented exercise programs. But this approach is unsuitable for many persons, and in such instances clinicians and patients need to agree upon what they *are willing* to do. If they will walk around the block once a day, then walk around the block. If they will swim, then swim. What you *do not* want to do is *tell* the patient they must obtain a gym membership and engage in 6 to 10 hours per week of rigorous physical activity—wherein afterwards, they often do nothing. Some type of an agreement must exist between patient and clinician as to what exactly they will do. Once that agreement is made, then the clinician should implement metrics of accountability, as well as back-up plans when terms of the agreement fail.

Dr. Jones: Most important, the patient needs to be honest. What will you do? Where will you do it? How frequently will you do it? And if you find that they will agree to exercise, they need to agree upon times and durations of exercise. Exercise must be for a *minimum* of 5 days a week—optimally, *every* day—for *at least* 30 minutes a day.

Dr. Bays: An exercise written prescription helps reduce ambiguity and may be perceived as more "official" by the patient and the patient's support system of family and friends.

Dr. Ballantyne: Correct, and I do write it down. Exercise for 30 minutes, 5 to 7 days a week, with a target of about 3 hours a week. Usually, it is walking because most people can do that. The motivation is that a loss of 5% to 7% of body weight reduces the risk of DM by two-thirds, which would be 10 to 14 pounds in a 200 pound person. Patients really respond to that: "Wow—two-thirds! I've done that before and I can do it again."

Dr. Friedewald: Thirty minutes, 5 to 7 times a week, is a reasonable minimum of exercise?

Dr. Jones: Yes, a reasonable minimum.

Dr. Ballantyne: A little exercise is good, but more is better, especially with weight loss. Weight loss can reduce the DM risk by as much as 80 to 90 percent. Just get them to agree on some program to get started. People are motivated by success. Realistic goals, when achieved, are far more motivating than some lofty target that is unattainable. A lot of people are very unrealistic. They say, "I want to lose 30 pounds." That is wonderful, but if you can lose only 10 pounds over the next period of time, that is terrific success. Realistic targets are key.

Dr. Bays: Recently, the National Lipid Association published a consensus statement on the relationship between adiposity and dyslipidemia.[8] It includes an extensive discussion about nutritional intervention and increased physical activity, and how these affect the lipid profile. The bottom line is this: appropriate nutritional and physical activity intervention improves many lipid and other metabolic parameters.

Dr. Friedewald: Why do we need a new drug for treating elevated TGs?

Dr. Jones: You might assume that the drugs we have discussed thus far are not effective enough, and that is not true. The problem is that using these medications is often challenging, such as the side effects of niacin, which make this drug very difficult to use. In addition to the adherence problems with niacin, it increases the blood sugar in some patients and it can also increase the uric acid. Fibrates—especially fenofibrate—can increase the serum creatinine, an effect that is usually benign and reversible, but it can raise concern, especially in patients with preexisting chronic kidney disease. Omega-3s—particularly if they contain

eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—may raise the LDL-C in patients with higher baseline TGs. Thus, there is a need for a drug that does not affect creatinine, blood sugar, or uric acid, can be used in patients with chronic kidney disease, and is complementary to existing drugs.

Dr. Friedewald: And that brings us to EPA, which we will focus on for the remainder of the discussion.

Dr. Ballantyne: EPA and DHA have been used for a number of years in treating patients with elevated TGs. They elevate the LDL-C level in people with very high TGs. There have been some small studies that looked at the issue of lipid changes, and in those studies, it appeared that there was not much of an LDL-C change with use of EPA. In the Japan EPA Lipid Intervention Study (JELIS)[9] using what is called a PROBE (Prospective, Randomized, Open-label, Blinded Endpoints) design, EPA or a placebo was given to patients who were taking pravastatin, and there was a significant reduction in secondary major coronary arterial disease events in patients taking EPA. The dose—600 mg, three times per day—however, was suboptimal for lowering TGs. JELIS showed that EPA might be a good new option in treating patients with elevated TGs, especially since it did not elevate the LDL-C. Further, EPA had already been shown to have a good safety profile.

Dr. Bays: The JELIS trial enrolled about 18,000 Japanese patients into a study that evaluated CV disease outcomes in persons treated with EPA. JELIS is the only trial ever performed in which a lipid-altering drug was shown to provide CV outcome benefits in patients already taking statins. One of the limitations of JELIS was the exclusive inclusion of Japanese participants, who may have genetic differences compared to a general population in the USA. Also, these patients were not chosen based upon elevated TGs at baseline, and the dose of EPA was only 1.8 grams per day. The statin doses in JELIS study participants were very low (e.g., pravastatin 10 mg per day; simvastatin 5 mg per day), and do not reflect statin doses typically prescribed in the USA. Nonetheless, the favorable outcome data with EPA was one of the reasons behind a clinical trial development program of EPA in a more general patient population. The MARINE (Multi-center, Placebo-controlled, Randomized, double-blinded, 12-week study with an open-label Extension) trial evaluated patients with TGs $\geq$500 mg/dl.[10] Compared to placebo, EPA reduced TGs by 33%, and significantly reduced non−HDL-C, lipoprotein-associated phospholipase A2, VLDL-C, and total cholesterol. Two surprising results of MARINE were a reduction in serum apoB and failure of LDL-C to rise.

Dr. Friedewald: Why were the apoB and LDL-C results a surprise?

Dr. Bays: They were a surprise because prior studies of EPA plus DHA showed little change in apoB, and in patients with very high TGs at baseline, EPA and DHA increased LDL-C by as much as 45%.

Dr. Jones: There were similar precedents of LDL-C increases in fibrate trials as well. These increases were not specific for any particular drug that lowered very high TGs. What we did not understand was the LDL-C increases were not due to increases in particle number; rather, they were caused by increases in particle *size*. As TG clearance improved, LDL-C particles enlarged, so the cholesterol content increased but the particle number really did not change much. Thus, the baseline TG determined what happened to LDL-C.

Dr. Friedewald: MARINE involved a mixture of populations from many countries. Did the results vary among countries?

Dr. Bays: This study was world-wide, conducted in the United States, South Africa, India, Russia, Ukraine, Finland, Germany, Italy, and The Netherlands. I am unaware of published data comparing the results of this study based upon country.

Dr. Friedewald: After MARINE came the ANCHOR study.[11] What did you learn from ANCHOR?

Dr. Ballantyne: ANCHOR addressed the use of EPA in patients with TGs in the 200 to 500 mg/dl range, and who were taking statins. This is the more common type of patient in the usual clinical setting—the patient who is at increased risk of CAD.

Dr. Jones: And, in contrast to the JELIS trial, statin doses were much higher.

Dr. Ballantyne: Patients in ANCHOR were randomized to placebo or EPA, 2 grams or 4 grams per day. Compared to placebo, with 4 grams of EPA the TGs fell by 22%. ANCHOR was designed to show noninferiority—that is, LDL-C would not go up compared to placebo, and it did not. Rather, LDL-C fell by an average of 6%. Non−HDL-C, apoB, and CRP also decreased. Thus, there were multiple benefits.[12]

Dr. Bays: Given the unexpected lipid results with regard to EPA's effects on LDL-C and apoB, ANCHOR is particularly important because it validated the lipid efficacy data from MARINE.

Dr. Jones: I want to emphasize that, in addition to the favorable results from both MARINE and ANCHOR, the problems that we mentioned earlier—increases in blood glucose, uric acid, creatinine (which can occur with fenofibrate)—were not seen with EPA. Thus, the safety aspect of EPA differentiates this drug from other drugs for treating elevated TGs.

Dr. Bays: These trials also showed that EPA produced no changes in liver enzymes, and at the 4 gram dose, did not elicit reports of eructation or "fishy burps" that often occur with omega-3s.

Dr. Friedewald: I assume patients in MARINE or ANCHOR did not have levels of TGs that are associated with pancreatitis, so that aspect was not studied?

Dr. Jones: That is correct. Patients at risk for pancreatitis were not admitted to the trial.

Dr. Ballantyne: An alert is set up so that at some point—for example above a set TG level—the patient is notified. There is an ethical concern to notify patients when they get into a danger zone.

Dr. Friedewald: To summarize, both the MARINE and ANCHOR trials showed EPA safety and efficacy in lowering TGs.

Dr. Ballantyne: Correct.

Dr. Friedewald: What about hard outcomes?

Dr. Ballantyne: MARINE and ANCHOR were lipid surrogate studies, looking at lipid efficacy, drug safety, and drug tolerability. The other reason that the ANCHOR trial

was done was to help guide decisions in designing future outcome trials, particularly what populations should be studied. They were the forerunners to REDUCE-IT (Reduction of Cardiovascular Events with EPA—Intervention Trial).[13] The goal of this ongoing trial is to determine whether EPA reduces events in high-risk individuals with elevated TGs who are being treated with evidence-based therapy on a statin. Patients are being treated with EPA 4 grams per day or a placebo.

Dr. Jones: This is particularly important because we have yet to find anything that can be added to a statin that provides incremental outcomes benefit. The 2 trials (AIM-HIGH[14] and HPS2-THRIVE[15]) in which niacin has been studied did not target patients with hypertriglyceridemia, so they were unhelpful in the use of niacin when added to a statin.

Dr. Ballantyne: And they also showed no benefit.

Dr. Jones: The ACCORD trial[16] looked at patients with DM in whom fenofibrate was added to a statin, but ACCORD did not recruit a sufficient number of patients with high TGs. Analysis of one prespecified subgroup suggested more benefit in patients with type-2 DM given a fibrate with baseline high triglycerides (>200 mg/dl). So we are hoping REDUCE-IT will provide data about whether there is real incremental benefit in high-risk patients of a targeted strategy, on top of optimal statin treatment.

Dr. Bays: In addition to potential effects upon CV events, another reason a long-term outcome trial is needed is for a greater assessment of safety. Thus far, EPA has been proven very safe. Irrespective of causality, pooled MARINE and ANCHOR data suggest that arthralgias are the only significant adverse reaction. Pooled data found that 2.3% of EPA participants reported arthralgias, compared to 1% of persons given placebo.

Dr. Friedewald: How do you currently use EPA in your practice?

Dr. Jones: Patients with TGs >500 mg/dl need all the help they can get, so EPA is a logical first-line choice for them, in combination with a fibrate or niacin. For patients with TGs <500 mg/dl, EPA does not have an indication. However, ANCHOR tells us that if niacin or a fenofibrate are not tolerated or are contraindicated, and there is concern about the LDL-C, EPA may be considered.

Dr. Friedewald: The current indication for EPA is for use in patients with TGs >500 mg/dl, correct?

Dr. Jones: That is correct, but sometimes we must use the treatment tools that are available even when they do not fit within labeling. Thus, we sometimes are forced to use omega-3s in patients with TGs <500 mg/dl, particularly if they have contraindications to niacin or cannot tolerate it. Patients with chronic kidney disease must take a low dose fibrate. Under such circumstances I believe EPA is an option, even when it is not indicated according to current TG level criteria.

Dr. Ballantyne: Although EPA is currently indicated only for use in patients with TGs >500 mg/dl, application has been made to the Food and Drug Administration (FDA) for an indication based on the ANCHOR trial in which the drug would be indicated for patients with TGs from 200 to 500 mg/dl.

Dr. Friedewald: With all new devices or drugs, we first treat patients at the extremes of the conditions.

Dr. Ballantyne: EPA is safe, well tolerated, and has good efficacy. It is particularly useful in patients with high TGs in whom you want to avoid raising the LDL-C. It is particularly useful in patients with high TGs in whom you want to avoid raising the LDL-C. It nicely accommodates the old medical adage, "first, do no harm."

Dr. Friedewald: Does the presence of DM make you more or less inclined to prescribe EPA for elevated TGs?

Dr. Jones: Patients with DM are at high risk, so they will already be taking statins. The statin blunts any effect that pure EPA or EPA/DHA omega-3s may have on LDL-C. We do not, however, have evidence that treating moderately elevated TGs in type-2 DM with EPA on top of a statin is beneficial, even though that concept is attractive. I hope the REDUCE-IT trial will give us the information about whether there is incremental benefit of EPA added to a statin. Patients with type-2 DM are the classic population who need that extra help and incremental benefit in treating lipids.

Dr. Friedewald: Do you believe that by having EPA available, clinicians will pay more attention to TGs than they have in the past?

Dr. Jones: Yes. Part of our discussion in this Roundtable is trying to bring to the forefront what TGs tell us: they are a good marker of a disturbed lipid system in a high-risk patient. It is not only important to recognize high TGs but also to look beyond the TG level to see what the background underlying risk is, rather than just prescribing a statin and letting it go at that. Both lifestyle changes and combination drug treatments are important for CV risk reduction.

Dr. Bays: Another reason for more clinical focus on TGs is the uncertainty of the benefits of super aggressive interventions regarding other CV disease risk parameters (e.g., blood pressure, blood glucose, HDL-C). After optimal control of these CVD risk factors, treatment of the 1 remaining marker that may still provide further CV risk reduction is lowering TG levels. But as with these other CV risk factors, we will not know this with certainty until after REDUCE-IT is completed. The time for this type of trial is long past due.

Dr. Friedewald: Accepting the reality that the outcomes results of REDUCE-IT are a few years away, what do you tell your patients concerning why you are prescribing EPA? The current justification is based on conjecture, which is logical but unproven, and TGs do not cause symptoms, so how are they going to benefit? We have to be treating more than a laboratory value in the eyes of the patient.

Dr. Jones: We will only get that answer from REDUCE-IT, which is being done with EPA. So while I believe there is benefit in the TG level in telling me what else I need to do in high-risk patients, the clinician should feel comfortable with a safe and effective medication, such as the natural product EPA, as an add-on, while awaiting the outcomes from REDUCE-IT. That is about all I can tell the patient.

Dr. Friedewald: If you believe there is a reasonable possibility that REDUCE-IT will show CV risk reduction in patients with elevated TGs, it would seem to me that is a good reason for a patient to want to take EPA, and for the clinician to prescribe it.

Dr. Jones: I do believe it is a possibility, although the incremental benefit is likely to be small—perhaps in the area of 10% added benefit.

Dr. Bays: While we would like to have definitive clinical trial outcome data for everything we treat, the fact is that until data are available, we do the best we can with the evidence we have. That is the basis behind guidelines and recommendations. Included in existing guidelines are recommendations for reductions in LDL-C, non−HDL-C and apoB. EPA reduces non−HDL-C and apoB, and in some patients, may lower LDL-C. It also reduces CRP levels, which many believe is important in CV risk reduction.

Dr. Friedewald: But "apoB" has no meaning to most patients. Heart attack and stroke, however, do have meaning, so it is likely patients will ask whether their risk for those events will be less with EPA.

Dr. Bays: If apoB can be explained as representing the number of particles that help cause atherosclerosis, then maybe it would be more understandable by patients. But at minimum, I believe most clinicians who routinely treat lipid levels recognize the importance of particle number, even if they do not routinely order this test in clinical practice.

Dr. Ballantyne: Let's put it this way. Your patient has had a heart attack and has been on a statin. The patient asks, "My TGs are high, and my non-HDL cholesterol is high. Does that put me at increased risk of having another heart attack?"*The answer is yes, it does*. "Is there anything more I can do about that?"*Yes, there is.* "But will EPA reduce my risk for another heart attack?"*I don't know*. "Is it safe?"*Yes*. "Could it have a benefit?"*There is a study being done to see whether it has a benefit, and nobody would do a study unless they thought it could have a benefit.*

In reality, each conversation is highly individualized, and a lot of it is about each patient's unique risk and their motivation to reduce the risk.[12]

Dr. Bays: I believe REDUCE-IT results will provide clarity.[13] It is usually more helpful to explain the potential benefits and risks of an intervention when the data is available to support this explanation. While no one can know the results of REDUCE-IT before the trial is completed, in the interim, if a patient has very high TG levels ($\geq$500 mg/dl) then EPA is a treatment option that lowers TGs—which is its treatment indication. Clinical trial data also suggest that in statin-treated patients with TGs of 200 to 500 mg/dl, EPA lowers TGs, non−HDL-C, lipoprotein-associated phospholipase A2, VLDL-C, and total cholesterol. EPA may also reduce LDL-C, apo-B, and CRP.

Dr. Jones: The only trial suggesting that EPA on top of a statin provides additional benefit is the JELIS trial, in which it was only effective for secondary prevention in patients with stable CAD. There were some primary prevention patients in the trial but they did not have significant benefit. Thus, there is a precedent for secondary prevention in patients with established heart disease and, for this reason, I believe that REDUCE-IT—which includes secondary prevention in high-risk patients—could end up showing incremental benefit.

Dr. Friedewald: You used an interesting term—that EPA is a "natural" treatment. The word "natural" is a good buzz word these days; is that why you use it?

Dr. Jones: Yes, "natural" conveys an element of safety for many people. When you mention omega-3s, you are talking about fish oil, and patients understand that. And they see it as a "more natural" product. The same thing is true with niacin, because it is a vitamin. Patients gravitate toward the "natural" approach to health, so this wording is helpful.

Dr. Bays: This is a double-edged sword, however. These days, when you prescribe a drug, the first thing patients do when they return home is go to the Internet to read about the drug. Drugs are often characterized in unfavorable, untrue manners. For example, if the Internet is your only source of information, you might believe statins are among the worst drugs a clinician can prescribe, with all risk and no benefit. Thus, venturing into the World Wide Web often causes patients to pause before starting or maintaining drug therapies. Conversely, the Internet is generally favorable to omega-3 fatty acids, with a widely reported number of health benefits—many of which would benefit from definitive clinical trials. But the point is, many patients just feel better if they are taking a "natural" product. So if the clinician observes that lowering TG levels in patients with very high TG levels reduces the chances of pancreatitis, and/or the clinician believes that long-term omega-3 fatty acid administration is in the best health interest of the patient, then to the extent that the "natural" label reinforces a sense of safety, this use of the term is warranted.

Dr. Friedewald: Dr. Ballantyne, I am going to read a statement you made in an *AJC* Editor's Roundtable in the year 2008,[17] to see if your position about TGs has changed over the last 5 years. The question then was, "How do you approach the patient with high triglyceride?" Here was your answer:

"One approach is to use some combination of fenofibrate, niacin, omega-3s, or all together, which usually causes the LDL-C to rise, and a statin is then added to the regimen. The other approach is for patients already taking a high-dose statin and they still have high triglycerides. In such cases, a low 48-mg dose of fenofibrate might be very effective in lowering their triglycerides. That effect also has not been studied, but I encourage physicians to try low-dose fenofibrate in combination with a statin when the triglycerides remain elevated."

Dr. Ballantyne: For patients with already taking statins and TGs >200 mg/dl and low HDL-C, I recommend fenofibric acid or fenofibrate, so with that modification, I stand by my 2008 statement.

Dr. Jones: I might add that in 2008, JELIS had not been published, so safety and efficacy data about EPA were not available then. Today, however, I suggest that you could be confident in also recommending omega-3s, including EPA, for such patients.

Dr. Friedewald: Thank you.

Disclosures

The authors have no conflicts of interest to disclose.

1. Miller M, Stone N, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, Goldberg AC, Howard WJ, Jacobson MS, Kris-Etherton PM, Lennie M, Mazzone T, Pennathur S. Triglycerides and cardiovascular disease:

a scientific statement from the American Heart Association. *Circulation* 2011;123:2292−2333.
2. Bays HE. Adiposopathy. Is "sick fat" a cardiovascular disease? *J Am Coll Cardiol* 2011;57:2461−2473.
3. Bays HE, Gonzalez-Campoy JM, Bray GA, Kitabchi AE, Bergman DA, Schorr AB, Rodbard HW, Henry RR. Pathogenic potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. *Expert Rev Cardiovasc Ther* 2008;6:343−368.
4. Bays H. Fish oils in the treatment of dyslipidemia and cardiovascular disease. In: Kwiterovich PO, editor. The Johns Hopkins Textbook of Dyslipidemia. 530 Walnut Street Philadelpha PA.
5. Bays HE. "Sick fat," metabolic disease, and atherosclerosis. *Am J Med* 2009;122:S26−S37.
6. Bays HBC. Adiposopathy: why do adiposity and obesity cause metabolic disease? *Future Lipidol* 2006;1:389−420.
7. Maki KC, Bays HE, Dicklin MR. Treatment options for the management of hypertriglyceridemia: strategies based on the best-available evidence. *J Clin Lipidol* 2012;6:413−426.
8. Bays HE, Toth PP, Kris-Etherton PM, Abate N, Aronne LJ, Brown WV, Gonzalez-Campoy JM, Jones SR, Kumar R, La Forge R, Samuel VT. Obesity, adiposity, and dyslipidemia: a consensus statement from the National Lipid Association. *J Clin Lipidol* 2013;7:304−383.
9. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K; 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;369:1090−1098.
10. Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, Paresh N, Soni PN. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multicenter, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] Trial). *Am J Cardiol* 2011;108:682−690.
11. Ballantyne CM, Bays HE, Kastelein JJ, Stein E, Isaacsohn JL, Braeckman RA, Soni PN. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR Study). *Am J Cardiol* 2012;110:984−992.
12. Bays HE, Ballantyne CM, Braeckman RA, Stirtan WG, Soni PN. Icosapent ethyl, a pure ethyl ester of eicosapentaenoic acid: effects on circulating markers of inflammation from the MARINE and ANCHOR studies. *Am J Cardiovasc Drugs* 2013;13:37−46.
13. A study of AMR101 to evaluate its ability to reduce cardiovascular events in high risk patients with hypertriglyceridemia and on statin (REDUCE-IT). *http://clinicaltrials.gov/show/NCT01492361*. Accessed on 7-25-13.
14. The AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;365:2255−2267.
15. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J* 2013;34:1279−1291.
16. The ACCORD Study Group. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med* 2011;364:818−828.
17. Friedewald VE, Ballantyne CM, Davidson MH, Guyton JR, Roberts WC. The Editor's Roundtable: lipid management beyond statins—reducing residual cardiovascular risk. *Am J Cardiol* 2008;102:559−567.