The Editor's Round Table: Current Perspectives on Triglycerides and Atherosclerosis

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Despite several decades of research about triglycerides and atherosclerotic cardiovascular disease, controversy still surrounds the question whether triglycerides are more than a biomarker and play a direct causative role in atherogenesis. In this Editor's Roundtable, a panel of leading lipid experts was invited to address this question and several closely related issues about triglycerides, including:

- The shift in thinking about elevated triglycerides rather than low levels of high-density lipoprotein cholesterol (HDL-C) as an important biomarker for atheroscerlosis.
- The emerging role of genomics in understanding dyslipidemias.
- The role of omega-3s in treating hypertriglyceridemia.

Dr. Friedewald: Do clinicians pay sufficient attention to elevated triglyceride (TG) levels?

Dr. Weintraub: No. They do not get the respect that they deserve. Historically, there has been ample opportunity to realize the impact of TGs, particularly in studies involving concomitant TG and cholesterol elevation. For example, the PROCAM (Prospective Cardiovascular Münster) study[1] and the Paris Prospective Trial,[2] which were conducted over 2 decades ago, identified significantly increased cardiovascular (CV) risk when TGs and total serum cholesterol were high. Retrospective meta-analyses of these studies show that TG-lowering drugs, such as niacin and fibrates, are effective in reducing CV risk among persons with elevated TGs.

Dr. Jones: There is a tendency among clinicians to assume that TGs reflect more whether a person is fasting or nonfasting at the time of blood sampling. Too often, physicians' reactions to elevated TGs are to attribute them to nonfasting states and then simply repeat the tests while patients are fasting. Then, if the TGs are not elevated while fasting, they disregard their importance and proceed with a treatment focus on only low-density lipoprotein cholesterol (LDL-C). Thus, TGs are often incorrectly regarded as nothing more than a function of eating, but this is a much more complex issue.

Dr. Friedewald: How much of the failure to pay attention to TGs is due to patients' failure to press their doctors about their importance? They know a lot about cholesterol, but patients almost never inquire about their TGs.

Dr. Weintraub: I agree, but patients parrot what they read in newspapers and other lay publications, which constantly reiterate the importance of LDL-C. The reality is that combined increased TG and LDL-C increases atherosclerotic risks. In Europe, however, much more attention is paid to TGs.

Dr. Jones: When I first entered the lipid field 35 years ago, there was a huge interest in the relation of TGs to CV disease, based on postprandial studies, and it was believed that postprandial handling of TGs was very important. However, postprandial TG evaluations are impractical in the usual clinic setting. However, we are coming back to realize that TGs are important in CV risk, whether measured in fasting or nonfasting states.

Dr. Weintraub: The first time I got involved with lipids was in the Helsinki Heart Study[3] at the end of the 1980s, and what struck me was the population that they were describing were the same people I saw in clinic whose first part of their bodies that came through the door were their bellies. They clearly had the metabolic syndrome or atherogenic dyslipidemia, and many of them did not have elevated total cholesterol levels, defined as >220 mg/dl at that time; rather, they had elevated TGs. Sometimes at Bellevue, we did not know whether they were fasting, but their HDL-C levels were low, they were often hypertensive, and many of these patients had CV disease. Whether patients are fasting or nonfasting is important to know, nevertheless. I often ask patients to come in not fasting. People are postprandial for much of the time, so fasting lipid levels are not what their endothelium is usually exposed to.

Dr. Friedewald: Are TG measurements gaining importance with the increasing incidence of obesity and resulting type-2 diabetes mellitus (T2DM)?

Dr. Jones: Yes, definitely, and this includes obesity in adolescents and young adults as well, along with increased prevalence of T2DM. Behind all of this is the process of insulin resistance, and insulin resistance drives a lot of the problems of TG handling in the body. Insulin resistance increases hepatic overproduction of TG-rich lipoproteins, which we call very low-density lipoproteins (VLDLs), and insulin resistance also reduces their clearance by decreasing the lipases responsible for clearance. Thus, there are patients who are obese and who have diabetes mellitus who, through insulin resistance, have an overproduction of TG-rich

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This discussion took place on June 12, 2015, in Chicago, Illinois.

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

See page 1702 for disclosure information.

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0002-9149/16/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2016.02.025

lipoproteins and decreased clearance that causes elevated fasting and postprandial TG levels. Hepatic overproduction of TGs and insulin resistance also are part of this process, which coalesce to form the metabolic syndrome. Patients with insulin resistance are easily identified in the clinic. They have high TGs, low HDL-C, impaired fasting glucose, elevated blood pressure, and central adiposity manifest by increased waist circumference. This relationship of TG-rich lipoproteins with CV disease risk and obesity was described in a Danish study published in Circulation Research.[4] As we would expect, LDL-C was a strong predictor, but fasting and nonfasting remnants and TG-rich lipoproteins, obesity, and hypertension were predictors as well—all components of the metabolic syndrome and insulin resistance.

Dr. Friedewald: Why are the Europeans ahead of the USA in studies of TGs given the greater prevalence of obesity in the USA?

Dr. Weintraub: We are much more fixated on LDL-C in the USA. And there have been arguments among the different research interests in the USA about how to study atherogenic lipoproteins. As a result, doctors are confused, and where there is confusion, there is a tendency to do nothing.

Dr. Roberts: As a cardiologist, I am not primarily interested in treating obesity—even though I should be. As a CV risk factor, TGs are not as amenable to treatment as LDL-C because fibrates and niacin are not as easy to take and do not receive as much attention as the statins (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors). As a result, we are properly treating only about one-third of the people in the USA who should be treated for abnormal lipids.

Dr. Friedewald: Explain the shift in thinking regarding the relative importance of low HDL-C versus elevated TGs as biomarkers for atherosclerotic disease.

Dr. Weintraub: Among lipid specialists, there has been an entire paradigm shift in the way we view lipids. For a long time, we were preoccupied with HDL-C, especially about failed trials using niacin and cholesterol ester transfer protein (CETP) inhibitors. As a result, we are now taking another strong look at TGs, especially their genetics. The Mendelian genetics for HDL-C show only 6 of the polymorphisms to be active, and 3 of them predict LDL-C characteristics as well. In contrast, there are numerous gene mutations involved with apolipoprotein (apo) C III that change TG levels and have a strong impact on atherosclerotic risk; this is very hard to overlook. Along with the data about apoC III and the increasing understanding about alternative measures to lower TGs, such as treatment with omega-3 fish oils, we are seeing a reawakening about the importance of TGs.

Dr. Jones: I was never a big HDL-C fan although I have long recognized that many patients who had low HDL-C also had high TGs. In the past, when investigators did a prospective evaluation, they concluded that the risk of low HDL-C is stronger so the low HDL-C is predictive and the high TGs are not because if you correct for the low HDL-C, the TGs disappear. Thus, again, the importance of elevated TGs was discarded and low HDL-C was the focus. Today, however, we know that what is important is the metabolism and the relationship between the overproduction of TG-rich lipoproteins, which are apoB-containing lipoproteins and are atherogenic, and their association with remodeling of HDL-C that automatically produces a lower HDL-C. As we have learned more about the genetics responsible for this relationship, we now know that it is the genetics that are responsible for high TGs and the cholesterol remnant TG particles, which is the true mediator. Even with Mendelian genetics, when you try to control for the HDL-C, it becomes insignificant and TGs remain the strong predictors.

Dr. Weintraub: When TGs rise, HDL-C falls and there is also remodeling of HDL-C to the point that HDL-C function may change. I still believe that there is a link between TGs and HDL-C, so we have not made a sudden left turn in our view of lipids and left practicing physicians confused. The science about the co-relationships between HDL-C and TGs has not changed. We just understand those relationships better and now view HDL-C as a biomarker. And TGs add more functionality to our understanding in that they pose a logarithmically higher and accelerated risk of atherosclerosis.

Dr. Mason: Regardless of whether TGs are biomarkers or causes of atherosclerosis, we have to consider how they affect the most integral mechanisms of atherosclerosis, such as inflammation, oxidative stress, and endothelial dysfunction. A variety of experimental and clinical studies support the concept that elevated biomarkers of inflammation more often occur in the presence of high TGs. Within just hours after a fatty meal, there is evidence of significant abnormal vasodilation and endothelial dysfunction. And TG-rich lipoproteins are an excellent substrate for oxidative damage, which then further contributes to inflammation and oxidative stress and ultimately, to plaque development. That we can directly link TGs to mechanisms of atherosclerosis argues persuasively that TG elevation is not just simply a bystander but a very important contributor to disease.

Dr. Friedewald: How do statins fit into this discussion about TGs?

Dr. Jones: Statins treat dyslipidemias and they are and should be the standard of care for individuals who are at increased risk. Statins primarily lower apoB-containing lipoproteins. They do a fabulous job in lowering LDL-C particles, which are major apoB-containing lipoproteins and are proven to reduce CV events as model therapy. In patients with mixed lipid problems involving other apoB-containing lipoproteins like VLDL and VLDL remnant particles, they are apoB-containing, but the mechanism by which statins lower LDL-C is not as efficient in clearing those TG-rich lipoproteins. LDL-C is a downstream product of lipid metabolism, and the LDL-C receptor is responsible for LDL-C removal. TGs, however, are overproduced by the liver and there are also lipases, which are responsible for their progressive clearance. Statins do not affect overproduction of VLDL nor do they have any effect on lipases. So, while statins lower TGs to some degree, they never lower them as much as they do LDL-C or LDL-C particle numbers. We have therapies that reduce hepatic TG production, including omega 3s and fibrates, which also improve lipase activity. Lipoprotein lipase decreases the apoprotein CIII, which helps clearance as well. Two recent articles looked at residual TGs in patients treated with statins, and this was a combination of 2 studies. One of these studies was MIRACL (Myocardial Ischemia Reduction with

Acute Cholesterol Lowering TRIAL),[6] which was a post-ACS population trial, and the other was dal-OUTCOMES (A Study of RO4607381 in Stable Coronary Heart Disease Patients With Recent Acute Coronary Syndrome).[5] The highest tertiles and quartiles of TGs strongly predicted early CV adverse events on high-dose optimal statin treatment, so physicians need to be aware that while they should use statins in high-risk individuals, residual TG elevations are predictive of subsequent CV events.

Dr. Friedewald: Do you believe that even in the presence of very low LDL-C, TGs still have an atherogenic effect?

Dr. Jones: According to observations in these analyses, yes, but observations are not randomized trials. Nonetheless, these findings are consistent with the fact that TGs predict events in very high-risk individuals despite high intensity, optimal statin treatment.

Dr. Weintraub: These articles[5,6] demonstrated that there are both short- and long-term increased CV risks of elevated TGs. Due to the nature of the studies that we design, we get a lot of our information within 5 years, but longer observations are needed. For example, the PROCAM study lasted 8 years.[1] After a patient has seen me for 5 years, I do not declare success and stop treatment. The real power of risk modification may be in longer term outcomes. There were confirmatory data in the PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction) study,[7] which looked at high-versus low-intensity statin effects postacute coronary syndrome and found that, on treatment, TG levels predicted events even in patients taking 80 mg of atorvastatin with low LDL-C.

Dr. Friedewald: What do you regard as a low LDL-C?

Dr. Weintraub: Below 70 mg/dl.

Dr. Roberts: Part of the reason we did not concentrate on TGs in the past, but did focus on HDL-C, was that HDL-C is elevated by exercise, niacin, and alcohol, which I believe may be protective, but these are also associated with decreased LDL-C. When we looked at 2 genetic variants that only increased HDL-C, we found no association with coronary artery disease or other manifestations of atherosclerosis because we were always looking at a "mixed bag" of lipids. Those therapies not only increased HDL-C, but they also lowered LDL-C, so all of us fell into that trap to some extent. From a genetic point of view, a very small change in the plasma level of apoC or LDL-C is associated with 40% to 70% reduction in cardiac events, so we must keep in mind that both duration and intensity of therapy are important.

Dr. Jones: I agree that lifetime exposure is important because atherosclerosis is a lifetime process, and many times physicians intervene at the end of the line of this process, and we try to see impressive improvements in a very complex environment of atherosclerosis. If we could start interventions much earlier, we could probably prevent them from progressing to that point.

Dr. Friedewald: What is the role of heredity in hypertriglyceridemia?

Dr. Roberts: The role of heredity is well defined. Many epidemiologists in the 1960s and 1970s pointed out that about 60% to 70% of plasma lipid levels are genetically regulated. We have now identified over 42 common genetic variants that affect TGs. Thus, TGs, HDL-C, and LDL-C are all strongly related to genetics, and they all relate to adverse CV events. These genetic relations raise new therapeutic opportunities. I authored a recent article[8] in which we took all of the genetic variants, such as those for CAD, and found that with genetic variants, regardless of age at the time of testing, we can identify individuals very early in life who are going to tend to have elevated TGs or LDL-C. I am certain that in 5 to 10 years, we will be treating patients for a lifetime based on specific lipid-related genetic profiles.

Dr. Friedewald: Give us an example of how genetics affects patient care.

Dr. Roberts: There are many people who do not adequately respond to even maximum doses of statins. There are over 300 mutants involving the LDL-C receptor. This means that one in every 200 to 300 persons will have a mutant and will require a different dose of statin. Another example is that 70% to 80% of cholesterol is synthesized in the body, and this is under very tight genetic control. Thus, if you take those rare variants like apoC III and knock them out, you decrease the risk significantly, and by identifying that variant you know when beginning treatment that they will have to be treated differently. I believe, in addition to prescribing statins, we will some day be prescribing therapies for apoC III, which increases TGs. Another point is that when we say that TG remnants are causal, we are still talking about the cholesterol in the TG-enriched remnant. We still think it is cholesterol that is the ultimate culprit for both atherosclerosis and associated inflammation.

Dr. Jones: The genetics are consistent with the mechanisms we already understood about TG production and clearance. A lot of the genetics involve mechanisms responsible for clearing TG-rich lipoprotein, especially those that affect lipoprotein lipase like apoAV, apoC III, apoC II, and angiopoietin-like protein III and IV. We knew those were a part of the clearance of TGs. Defects that cause overproduction or underproduction or loss of function or gain of function, also overproduce TGs, with a higher risk like in the loss of function with apoC III. TGs are probably more responsive to environmental influences than is LDL-C.

Dr. Mason: The genetics reinforce what we believe in terms of the mechanisms of atherosclerosis. Non—HDL-C, TG-rich particles, and apoB are all essential to developing endothelial dysfunction and inflammation, so the genetics are reinforcing what we already understand and give us even more necessity to evaluate and understand those mechanisms. We also see how the Western diet, in light of these genetic changes, contributes to CV risk as it leads to insulin resistance, obesity, and T2DM.

Dr. Freidewald: What do the MARINE (the multicenter, placebo-controlled, randomized, double-blind, 12-week study with an open-label extension)[8] and ANCHOR[9] trials tell us about LDL neutrality, apoC III, and remnants?

Dr. Weintraub: The MARINE[8] and ANCHOR[9] trials were performed with a novel omega-3 fish oil that contained only eicosapentaenoic acid (EPA). MARINE studied people with TGs >500 mg/dl and ANCHOR studied people with TGs of 200 to 500 mg/dl. ANCHOR was populated by many persons taking statins, which provided some other interesting data. These studies showed EPA to be highly effective in lowering TGs in people with very high TGs.

However, such persons comprise <1% of the population, compared with 15% to 20% of the population having TGs >200 mg/dl, and one-third of the population having TGs >150 mg/dl. It is also important, although controversial, that EPA-only compounds appear to not increase LDL-C, which did occur with EPA/DHA (docoshexaenoic acid) compounds in previous studies; this effect has been attributed to the DHA component. Another important observation was that higher statin doses were associated with greater TG-lowering, which does not occur when fibrates are combined with statins. This sets a backdrop for a new event trial called REDUCE-IT (Reduce Cardiovascular Events in High Risk Patients With Hypertriglyceridemia and on Statin) trial,[10] which will be the first study of people with increased CV risk whose TGs are high, and who are on statin background therapy and receiving a fish oil.

Dr. Mason: A disproportionate reduction in smaller LDL-C particles was observed in the ANCHOR Trial in persons treated with EPA, so somehow, omega-3 fatty acid therapy preferentially reduces the more atherogenic LDL-C subgroup, probably by improving more efficient clearance. There is a simultaneous reduction in oxidized LDL-C, which cannot be cleared very well by interfering with LDL-C oxidation. Targeting small dense LDL-C is a very promising outcome. ANCHOR also demonstrated a very nice reduction in apoC, along with C-reactive protein (CRP) and other inflammatory markers.

Dr. Jones: Oxidized LDL-C may be important, but it is clear that when omega-3s are added to a statin in persons with TGs in the 200 to 500 mg/dl range, the remnant VLDL-C goes down significantly, and genetics have proven that those remnant particles are causative in atherosclerosis. Thus, it may not matter that the LDL-C does not go down any more.

Dr. Mason: It is also reassuring that when ANCHOR investigators broke it down to even higher risk patients in that group, such as those with DM, the benefit was proportional to the extent of hyperglycemia. Thus, persons who are sicker and at higher risk have better effects with treatment.

Dr. Jones: And it may be that remnants are not picked up in usual lipid panels. An outcome trial called JELIS (Japan EPA Lipid Intervention study),[11] in which an omega-3 and EPA only were added to a statin found that the use of only EPA reduced all CV events by about 19% which was significant.

Dr. Friedewald: What is the evidence that elevated TGs and TG-rich proteins are not just biomarkers; rather, they have a causative role in atherogenesis?

Dr. Jones: The best evidence at this time comes from the Copenhagen City Heart Study,[12] the General Population Study,[13] and the Copenhagen Ischemic Heart Disease Study.[14] They clearly found 2 things. First, elevated fasting TG is associated with a 60% increased risk of CV events in the highest quartile compared to the normal level. Second, nonfasting TG-rich lipoproteins have a similar association with high risk. It does not matter whether you look at fasting or nonfasting TGs. Thus, when a patient asks whether they should be fasting, the answer should be "no," and the TG measurement should be made regardless of when the last meal occurred. If nonfasting TGs are abnormal, the risk is increased. If they are abnormal when fasting, that indicates increased risk as well. On the other hand, if they are completely normal 2 hours after eating, that is low risk.

Dr. Friedewald: What is the potential pleiotropic biological role of the omega-3s and EPA in their atherosclerotic pathway, and how does the new REDUCE-IT trial[10] address this question?

Dr. Mason: Some of the early TG-lowering trials with fibrates and niacin were very positive, but when combined with a statin, there was no further benefit with respect to the risk of CV outcomes. The exception recently has been outcome improvement with adding ezetimibe to a statin. Another trial showing improvement when adding a drug to a statin is JELIS.[11] This was a large study in Japan in which patients were already on moderate statin use and were at high CV risk. EPA (1.8 g) was added to the statin, and there was a 19% reduction in CV events, even when including patients with normal TGs. This finding led to an intriguing question: could an omega-3 fatty acid be doing something we have not observed with other TG-lowering agents? Although the literature contains very compelling and intriguing evidence suggesting omega-3 fatty acids can interrupt certain pathways in atherosclerosis, there have been very few head-to-head studies with other TG-lowering agents. In the last few years, our laboratory compared an omega-3 fatty acid to niacin and to fenofibrates with respect to basic processes of atherosclerosis and found some intriguing differences that may explain the benefit in JELIS. In particular, we found that an omega-3 fatty acid like EPA is very effective in entering blood vessels and affecting vascular processes like endothelial function. However, we did not see those effects with niacin or the fenofibrates. We also observed that omega-3 fatty acids can interrupt oxidative damage to important lipoproteins, including small density LDL-C. There also may be some important so-called pleiotropic or non−TG-lowering related mechanisms of EPA that could help us understand why we saw a positive signal with JELIS. Our findings now must be confirmed in a larger multinational trial, and that is being done in the REDUCE-IT trial.[10] REDUCE-IT is very similar to the ANCHOR Trial,[9] using a high-risk population with TGs of 200 to 500 mg/dl and is placebo controlled. The current EPA dose is 4 g, which is much higher than the does used in the JELIS trial. REDUCE-IT is well underway, and the results should be available in 2018.

Dr. Weintraub: One of the intriguing aspects of JELIS is that in individuals with TGs ≥200 mg/dl, there was more than a 50% reduction in CV events with EPA. There are some issues that people take with the trial, but this result is as good as you can get.

Dr. Mason: In JELIS, they were all on statins and so on standard care, and in the ANCHOR Trial, some of the best effects with respect to reducing apoC were observed in patients taking high-dose statins. In our own laboratory research, we are seeing some synergies between the omega-3 fatty acids and statins as they relate to endothelial function, so they may adopt different but complementary pathways when they improve nitric oxide release and reduce inflammation.

Dr. Jones: In REDUCE-IT, if the TG level is not high enough, we may not see the effect that we want. I believe

that there are some pleiotropic effects that may be beneficial, but I also believe that TG-rich lipoproteins are also very contributory.

Dr. Roberts: When interpreting clinical trials going forward we are trying to assess the pebble by measuring the mountain because everybody is going to be on statins if they are receiving optimal lipid therapy, which lowers both the LDL-C and TGs. Thus, large sample size will be essential for valid results.

Dr. Friedewald: According to National Lipid Association Guidelines, fibric acid and DHA can elevate the LDL-C. How important is this effect on LDL-C in treating patients with elevated TGs, and how do you address this when using these agents?

Dr. Mason: This is very important. We do not want to raise LDL-C in dyslipidemic patients. There has been some suggestion that DHA reduces LDL-C receptor expression. Fibric acid also can adversely affect LDL-C metabolism. Thus, we need to be certain that drugs prescribed for lowering TGs have at least a neutral effect on LDL-C.

Dr. Jones: Some of the changes in LDL-C are different from those in particle numbers, which clinicians need to be aware of: LDL-C particles are smaller when TGs are very high. As TGs are lowered, LDL-C particle size increases. The number of particles may not change, but the cholesterol content may change, so when the cholesterol level in LDL-C seems to go up, the particle number may not go rise. Thus, it is very important that physicians understand that while using an omega-3 in people with significant hypertriglyceridemia, even when taking a statin, there will probably be no increase in the particle number.

Dr. Roberts: If the particle number does not rise, does CV risk remain unchanged?

Dr. Jones: In my opinion, yes.

Dr. Weintraub: The real appeal of prescribing omega-3s is that it does not carry the same warnings as when co-prescribing a fibrate or niacin with a statin, which carries real risks, and is very disenfranchising to the prescriber. However, patients are not reluctant to take fish oil.

Dr. Jones: There are no drug−drug interactions with omega-3s to be concerned about, either.

Dr. Friedewald: What are your concerns about patients taking fish oil dietary supplements?

Dr. Mason: This is an interesting question since we see so many television commercials about the remarkable CV benefits of fish oil supplements. The challenge for consumers is which fish oil supplement to choose. We conducted our own independent tests of different widely used fish oil supplements, which we purchased in the store. We opened the capsules and measured how much actual omega fatty acid is inside, since the manufacturers attribute so much of the benefit to omega-3 fatty acid. We found some remarkable results. For example, levels of omega-3 fatty acid vary widely from 1 brand supplement to another, and patients do not necessarily know that by the number of capsules they are instructed to take. Some reported contents of only 90 mg, they actually contained a little less. Some contained as much as 700 mg. Thus, what people should purchase and how much they should take is difficult to answer. Persons with very high TGs are supposed to take 4 g, which is a lot of capsules. We estimated that, with 1 product 13 fish oil capsules would have to be taken to achieve 4 g, and with another, 44 fish oil capsules were needed to achieve a therapeutic dose. So, for patients with very high TGs, fish oil supplements are not a good alternative. Another of our findings involved the integrity of the omega-3 fatty acid because omega-3 fatty acids are polyunsaturated and thus highly susceptible to oxidative damage. If the omega-3 fatty acids are exposed to atmospheric conditions or oxygen for only a few hours, significant contamination or rancidity occurs, adversely affecting many of the mechanisms of action. These are serious issues confronting patients relying on omega-3 supplements, especially if they need them for pancreatitis or for very high TGs. We need better oversight of this industry, especially with regard to what manufacturers propose these supplements will do compared to what is actually in them.

Dr. Jones: What about over-the-counter krill oil supplements?

Dr. Mason: We studied those as well. Just in terms of clarifying the terminology, there is no over-the-counter fish oil. There are only prescription and supplement fish oils. With respect to krill oil, it does contain EPA and DHA but at much lower concentrations. They suggest less is needed because they are in a phospholipid-type format, but it does not matter what format or form EPA or DHA is in if it is in low concentration.

Dr. Weintraub: They appeal to some of the only things that patients disagree to, and one of them is the size and number of pills, and the other one is sometimes people will have bothersome eructations, which are less with the branded EPA medication as it is with others.

Dr. Mason: There are other problems with nonkrill oils. In addition to EPA and DHA, they contain dozens of other fatty acids. The most abundant fatty acid in one particular product was a saturated fat called palmitic acid. Another was myristic acid, which is another saturated fat. With all the saturated fats, I am convinced that they deliver more saturated fat than omega-3's. Certainly, no investigator would ever be allowed to do a study in which patients received more saturated fats than omega-3s, but that is exactly what these products do because they are coming right out of the fish without any purification or attempt to prevent oxidation.

Dr. Friedewald: Let's conclude with some practical advice for nonlipid experts in treating patients with elevated TGs.

Dr. Weintraub: First, I encourage them to look at their patients' TG levels and do not hesitate to measure TGs in the nonfasting state. They should recognize the importance of lifestyle, including diet, exercise, carbohydrate reduction, alcohol restriction.

Dr. Roberts: Clinicians should recognize that there are strong epidemiological, genetic, and clinical studies clearly documenting that increased TGs is a risk factor for heart disease.

Dr. Jones: Elevated TGs are part of a conglomeration we call metabolic syndrome, including insulin resistance, which is tied to obesity, lifestyle, and genetics. This is an opportunity for clinicians to address all these factors in which lifestyle is an increasingly important part of patient responsibility to make themselves healthier. Measurement of TGs and non−HDL-C, in addition to LDL-C, is an

important part of CV risk assessment. Both the National Lipid Association and the International Atherosclerosis Society endorse non−HDL-C diagnosis and treatment.

Dr. Mason: Non−HDL-C is very important because it links very well to atherosclerosis pathophysiology, so there is a compelling reason to screen and identify patients who have high TGs and to treat them. At this time, we rely heavily on lifestyle since we are still looking for compelling clinical outcome data for therapies, but we can modify elevated TGs through lifestyle. We should also look at the opportunities for newer therapies, such as omega-3 fatty acids, to eventually be possible treatments of choice.

Dr. Friedewald: When should a patient with hypertriglyceridemia be referred to a lipid expert?

Dr. Weintraub: When TGs are >500 mg/dl there needs to be prompt, efficient lowering of TGs to reduce pancreatitis risk. If the clinician is not comfortable with orchestrating the lifestyle, diet, and medication issues with TGs, a lipid expert should be consulted. For the larger number of patients with TGs at 200 to 500 mg/dl, if you are not comfortable, again, implementing diet and lifestyle, and balancing what may be 2 or even 3 medications, then that, too, would be a circumstance in which referral is indicated.

Dr. Roberts: I have a slightly different answer. It is time for us to really impress on practicing physicians that they should get into the game themselves, recognizing TG elevations can be complex. The data, however, are overwhelming that we can prevent a lot of heart disease based on our present knowledge and treatments, so primary care practitioners need to become more involved with TG treatment.

Dr. Jones: Patients with severe hypertriglyceridemia probably need a specialist who practices clinical lipidology because they usually have the associated health care providers necessary to help, especially dieticians and certified diabetes educators. But I agree with Bob that anybody can learn how to properly diagnose and treat these patients.

Dr. Mason: All clinicians should be able to treat patients except those with extreme forms of dyslipidemia.

Dr. Friedewald: Thank you.

Disclosures

Dr. Jones is a scientific consultant for Amgen, Sanofi/Regeneron and Merck and is Chief Science Officer for the National Lipid Association. Dr. Mason has received grant/research support from Amarin Pharma Inc., Pfizer and Novartis, and provides speaking and consultancy services (including receipt of honoraria) for Novartis and Amarin Pharma Inc. Dr. Roberts serves on the Advisory Board, Cumberland Pharmaceutical. Dr. Weintraub performs research for Amarin and Sanofi; is a consultant and/or serves on advisory boards for Amgen, Gilead, and Kowa. The other authors have no conflicts of interest to disclose.

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