Hypertriglyceridemia: Association or Causative for ASCVD Management?

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Introduction and Welcome

DR. ECKEL: Hi, everyone. I’m Bob Eckel, one of the course directors here for this certificate program in cardiometabolic medicine. And I’ve been privileged to be co-chair of the Cardiometabolic Health Congress now for 15 years.

The talk I’m going to be giving today is on hypertriglyceridemia, the association or causative issues that relate to atherosclerotic cardiovascular disease management. By the way, that’s a question. Is hypertriglyceridemia simply associated with atherosclerotic cardiovascular disease or in fact is it causative? And we’re going to be discussing that in detail.

My current or past appointments. Actually, I’m a Professor of Medicine and now emeritus in the division of endocrinology metabolism in diabetes and the division of cardiology at the University of Colorado Anschutz Medical Campus. And I’m also the former Charles A. Boettcher II Chair in atherosclerosis.

Here are my dualities of interest. Amarin, KOWA, Novo Nordisk, UpToDate, and WW or Weight Watchers.

The learning objectives are four in this presentation. The first is to discuss problems with the definition related to the prevalence and causes of hypertriglyceridemia. The second is to provide updates on if and how hypertriglyceridemia relates to atherosclerotic cardiovascular disease, using informative cardiovascular disease outcome trials. The third is to evaluate strategies for hypertriglyceridemia management and that relates to moderate degrees of hypertriglyceridemia and severe hypertriglyceridemia.

And finally, I’ve been asked to summarize the current science and management of levels of HDL cholesterol. This is an important topic I think to conclude this presentation in terms of the important relationship between HDL cholesterol and triglycerides.

Discuss Problems with the Definition Related Prevalence and Causes of Hypertriglyceridemia

The first topic again for us today is in fact discussing problems with the definition and related prevalence and causes of hypertriglyceridemia. I think it’s important to start to show this important inverse relationship between levels of plasma HDL cholesterol and plasma triglycerides. As you see, this is a strong inverse relationship which actually might be better magnified as ultimately a logarithmic transformation. This becomes a straight line.

But nevertheless, I think what you can see is people with higher levels of triglycerides defined here let’s say above 1.3 millimolar which by the way is around 120 milligrams per deciliter. People with high triglycerides are expected to have low levels of HDL cholesterol. But people with normal levels of triglycerides have a great degree of variability, but the slope is still downhill. In other words, when we see a patient with hypertriglyceridemia we should expect to see lower levels of HDL cholesterol.
Now, what’s the explanation for this inverse relationship between HDL cholesterol and plasma triglycerides? Well, first, the formation of larger more buoyant cholesterol-enriched HDL is dependent on the hydrolysis of triglyceride-rich lipoproteins by the enzyme lipoprotein lipase.

Here’s a cartoon to reflect this relationship. Here are the triglyceride-rich particles, the chylomicron, and the VLDL and these particles circulate in the systemic circulation. And ultimately, they identify themselves with lipoprotein lipase shown here in red which is an enzymatic activity that controls the hydrolysis of triglyceride into free fatty acids and monoacylglycerol from the triglyceride-rich lipoproteins. The LPL is present in most tissues around the body or perhaps is most relevant in cardiac muscle, skeletal muscle, and adipose tissue.

After this hydrolysis, these free fatty acids and monoacylglycerols are taken up locally by the variety of tissues that make LPL. And either they are stored locally such as in adipose tissue or they are used for oxidative metabolism such as in skeletal and cardiac muscles.

Now, part of this reaction relates to the transfer of surface lipids and that’s unesterified cholesterol and phospholipids from these triglyceride-rich particles to a smaller form of HDL called HDL-3 to a larger, more cholesterol-enriched form of HDL called HDL-2.

When lipoprotein lipase is low or triglyceride production is high there’s a relative defect in the conversion of these triglyceride-rich particles to ultimately free fatty acids and monoacylglycerol. And therefore, there’s a reduction and transfer of unesterified cholesterol and phospholipids from the surface of these particles which become redundant after this hydrolytic activity to HDL. And of course, HDL is a major cholesterol lipoprotein. Levels of HDL cholesterol tend to be reduced in that setting.

The second explanation is when hypertriglyceridemia is present. The HDL particles are more triglyceride enriched because there’s more triglyceride in all of the particles and that replaces some of the cholesteryl esters within triglycerides into the lipoprotein core. This second issue is a compositional issue that relates to this content of cholesterol in the HDL particle compared with a relative proportion of triglycerides in the particle.

And the third explanation relates to the catabolic clearance of HDL. When the HDL are triglyceride enriched they are more likely to be more rapidly hydrolyzed by hepatic processes and the ApoA1 which is the major protein of HDL excreted in the urine.

These are the classic and more formal explanations on why HDL cholesterol levels tend to be low when plasma triglyceride levels are higher.

Now, hypertriglyceridemia I think is the most difficult lipid disorder to evaluate and treat. Why is that? Well, the common disorders are not single genes. Ultimately, the acquired disorders are numerous. The clinical trials with triglyceride-lowering drugs have suffered and we’ll come back to that. They’ve suffered from design. They’ve suffered from the number of trials compared to the cholesterol-lowering trials or LDL cholesterol-lowering trials.

And the result, to a large extent, has been mostly hypothesis-generating. Is it the triglycerides themselves, the lipids themselves, or the triglyceride-rich particles that confer this risk for atherosclerotic cardiovascular disease or is it the company they keep such as insulin resistance, inflammation, and other players when triglycerides are elevated?
Ultimately, I’m showing this variability in fasting levels. If we look at the diurnal biological variability and triglyceride measurements, that can be for morning fasting to non-fasting at night or it could be from day-to-day biologic variability. Look at that variability. It’s 30% biological variability from any time of day to another versus from a daily basis where they’re fasting or non-fasting. And even the monthly biological variation is substantial up to nearly 21%.

Compare that now with ApoB, ApoA1, LDL cholesterol, HDL cholesterol, or total cholesterol either in the biologic variability on a diurnal basis or the monthly variability that relates to biological variability. These ultimately are coefficients of variations. They’re all below 10%. Whereas triglycerides are two to three to four times higher than that.

Now, ultimately, this whole variability of triglycerides may in fact relate to coronary heart disease. And these are studies that were carried out with Madiha Abdel-Maksoud here at the University of Colorado and published now a few years ago actually. It’s looking at when univariant analyses relate to log triglycerides to cardiovascular disease risk. There’s a bit of a nonlinear association, but when the multivariant analysis is studied over a number of days, weeks, months, and years we look at that as a risk factor for cardiovascular disease.

Look at this impact. A P-value that is really substantially low compared to what it would be if, in fact, just a log-linear or nonlinear transformation took place. This relates to other coronary heart disease risk factors which were used in the model, including LDL, baseline age, male gender, and log triglycerides meaning fasting triglycerides. This variability may be important in terms of how we think about how triglycerides relate to it. Notice I say relate to atherosclerotic cardiovascular disease events, specifically here coronary heart disease. There’s the strong P-value again.

Now, population data are skewed. I’m not going to get into that in more detail. When I mean skewed there’s a bell-shaped curve that has shifted to the right. And we’re going to get into definitions in a moment, but that shifting to the right means there are probably a lot more people at 400 than there are at 90 or 80. This is a shift to the right which relates to the skewing of the population.

The relations to coronary heart disease often fail to relate to the extent of elevations and we’ll see that from some of the cardiovascular disease outcome trial data.

And the big question comes up. What’s a normal triglyceride level? When I first entered this field decades ago, I used the term “100 plus age is the upper limit of normal.” But that really doesn’t fit now in terms of what the population data look like. I’m not sure we still know what a normal level is.

By the way, should it be fasting triglycerides or should we look at the - - data where the variability of triglycerides was a more important predictor or even maybe a non-fasting triglyceride level in terms of how it relates to atherosclerotic cardiovascular disease.

To really make this even a little bit more complex what I’ve chosen to do here is show three attempts by professional organizations to define hypertriglyceridemia. The American Heart Association and American College of Cardiology and multi societies in addition to those two organizations have defined normal as less than or equal to 175, moderate is 175 to 499, and severe or greater than or equal to 500 milligrams per deciliter.
Here’s the European Society of Cardiology and normal levels are under 150. And by the way, the millimolar concentrations are shown at the right. A mild to moderate elevation is 150 to 880. Look at this 880 compared to 499. We’re talking about a whole different biology in that area and severe above 880 or 10 millimolar concentration. And the Endocrine Society’s normal is under 150, mild is 150 to 199, moderate is 200 to 999, severe is 1000 to 1999, and very severe of greater than 2000. I think the only merit for defining severe and very severe is pancreatitis tends to occur more frequently in patients who have fasting triglycerides above 2000 than it does between 1000 and 1999. But still, it’s increased in this population here.

I’m going to opine and this is consistent to a large extent of what we share in UpToDate. Less than 150 is normal. Again, we could argue that point based on the CVOTs. Moderate hypertriglyceridemia is from 150 to 499. We would tend to agree with the American Heart Association and the ACC here. Moderate to severe is 500 to 999 and in UpToDate, which I co-authored with Bob Rosenson, we listed 880 simply because that rounds off to 10 millimolar. Biologically, there’s not much difference between 880 and 999. And severe defined is greater than or equal to 100.

This makes it a little bit simpler and helps to consolidate these various recommendations by the various societies. None are perfectly right and none are totally wrong. I think these are working guidelines on how to define hypertriglyceridemia.

Let’s look at the prevalence based on a fasting level of greater than or equal to 150 using the NHANES database between 2007 and 2014. The data here are reflected as percentages. Based on an overall prevalence, age greater than or equal to 20, we’re looking at about a 25 to 26% prevalence of triglycerides above 150. One-quarter of the population is hypertriglyceremic using this definition. And statin-treated patients are almost a third and that reflects I think the fact that statin-treated patients are more likely to have lipid disorders which may also include hypertriglyceridemia. And statin-treated patients whose LDLs are reduced we have a bit of lowering of triglycerides to around 27%.

But those with diabetes who are statin-treated are much more likely because of the insulin resistance and insulin deficiency that occurs in diabetes. Forty percent of patients with diabetes even though they’re statin-treated have triglycerides greater than or equal to 150. A little less than a third of people who are statin-treated and have atherosclerotic cardiovascular disease and those that are statin-treated with diabetes and atherosclerosis and diabetes ultimately have about a 6 or 7% reduction compared to diabetes in the absence of ASCVD.

And I think why that’s true, particularly in statin-treated and LDLs under 100 is moderate to high-intensity statins have an independent triglyceride-lowering effect. That’s what we’re seeing here and I think people with atherosclerotic cardiovascular disease who are on statins to get their LDLs under 100, at least a substantial portion of those patients who are on statin therapy.

**Hypertriglyceridemia & ASCVD Risk**

Where’s the background? Let’s now look at some evidence that relates to how triglycerides relate to atherosclerotic cardiovascular disease. And in part, we’re going to use informative cardiovascular disease outcome trials. I think we’ll direct some of that information to the next topic relating to the evaluation of strategies to treat triglyceride elevations.
The big question that she asked here. Does hypertriglyceridemia cause CVD? I think specifically, she should say atherosclerotic cardiovascular disease because cardiovascular disease is a blanket term used even to include hypertension sometimes. But it includes stroke, peripheral vascular disease, et cetera. Of course, peripheral vascular disease can relate ultimately to atherosclerosis to a large extent as can stroke, but we certainly know that some strokes are hemorrhagic and not prothrombotic.

And/or is increased TG simply a risk factor or is it association only? Is it causation or simply a risk factor by association only? Good question and I’m not sure we still have the final answer.

If we look at a meta-analysis here of some 262,000 patients published by Nadeem Sarwar in circulation. It was 15 years ago now. We’re looking ultimately at these studies that relate to the duration of follow-up, gender, the status of the fasting versus non-fasting triglycerides, or are the data adjusted for HDL? Let’s start down here. Because remember, this inverse relationship of HDL cholesterol to triglycerides is important when we’re thinking of causation. Maybe much of the hypertriglyceridemia associated with coronary heart disease risk occurs because the HDL cholesterol is lower.

But if we look at all these other explanatory variables that relate to those triglycerides or do triglycerides relate to coronary heart disease we’re left these be about the same. In this analysis, fasting looked a little stronger with the non-fasting, but basically, gender and duration had no effect with a risk ratio for the triglyceride coronary heart disease association of 1.7, and that includes the HDL cholesterol adjustment.

If you will, people who have triglycerides defined as above 150 have about a three-quarters additional risk or a 75% increased risk for a coronary heart disease event.

Now, if we look at elevated triglyceride levels in terms of the independent association with all-cause mortality and now, we’re looking at patients with established coronary heart disease. This is fairly short.

This is a 22-year follow-up of the bezafibrate infarction prevention study registry published in 2016. Bezafibrate is a fibrate that was used in European trials to a large extent. This drug is not available in the United States. And here we’re looking at people with triglycerides from under 100 to above 500. And we are looking at this curvilinear or at least gradient risk of having hypertriglyceridemia in people with established coronary heart disease in terms of now all-cause mortality. This tends to get our attention a little bit more, doesn’t it?

It relates to coronary heart disease incidence and it relates to all-cause mortality in people with established coronary heart disease. This looks like it’s something we should be paying a lot of attention to.

Now, first of all, let’s look at the atherogenicity of triglyceride-rich lipoproteins. This is a paper that I had the privilege to share with Ira Goldberg and Ruth McPherson. Now, it’s been 10 years ago. But this biology, by the way, has not changed.

What we’re looking at is the vascular lumen. And here is a cartoon again that shows the important relationship of lipoprotein lipase to the endothelial cells through the glyocalyx and bound to the GPIHBL binding protein. Ultimately, we’re looking at the lipolysis products generated by the hydrolysis of the triglyceride core of these particular particles.
One hypothesis is that this reaction, the hydrolysis of the triglyceride core, relates to the uptake of lipolysis products which could be fatty acids. But these could be other molecules contained within the particle that induces inflammation, modify vascular adhesion of toxic metabolites, and maybe prothrombotic.

This is the lipolytic toxin hypothesis which would perhaps relate to a direct effect of lipoprotein lipase on the hydrolysis of triglycerides and the downstream byproducts in triglyceride hydrolysis on the atherosclerotic plaque.

The second hypothesis is that the lipoprotein lipase reaction. Here it’s shown again LDL. And of course, this is the chylomicron, the bigger particle here on the right. The lipolysis of the LDL or even chylomicrons reduces the particle size to an ApoB containing remnant. I should point out here the remnant of chylomicron is not ApoB containing. It’s ApoE containing. And I should really correct myself. It has an ApoB protein, but this ApoB that the chylomicron carries is not sufficient to be recognized by ApoB receptors.

Let’s just say this chylomicron or VLDL remnant is an ApoB containing remnant that is now cholesterol-enriched. Remember, these triglyceride-rich particles are mostly containing triglycerides.

But now, after the hydrolysis, this remnant particle is cholesterol-enriched and now being smaller it can enter the extravascular space. Here it’s the products that enter the extravascular space, not the particle. But these remnant particles are carried through the vascular space and can ultimately induce inflammation of adhesion molecules and coagulation just like the lipolytic toxic hypothesis can be an explanation for atherosclerosis. But this remnant particle now carries a lot of cholesterol and the macrophage loves cholesterol and takes up these particles and ultimately contains cholesterol. And ultimately, it esterifies that for the cholesteryl ester storage that relates to the atherosclerotic plaque.

I think we have either causation or the downstream particles that are cholesterol-enriched that relate to the atherosclerotic process. We don’t know for sure, but both of these are still reasonable hypotheses about how triglyceride-rich lipoproteins relate to atherosclerosis.

Now, this is a complicated slide recently published by Karin Bornfeldt from the University of Washington. Let me take you through this very quickly. Here’s the liver with fatty acids reaching the liver that make triglycerides in the liver secreted as VLDL and VLDL has a series of apolipoproteins on its surface. Here’s the lipoprotein lipase reaction, the VLDL remnant, and here’s the remnant is taken up in the artery. And here we have the chylomicron formed in the gut. This is a triglyceride-rich particle larger than VLDL that is hydrolyzed down to a chylomicron remnant. No ApoB-100 like is present in VLDL. But this particle is also cholesterol-enriched and can return to the systemic circulation and liver cholesterol to the atherosclerotic plaque.

Now, notice the question marks around whether these particles themselves, first of all, have access or whether they themselves through the toxic lipolytic process deliver products of lipolysis that may be to the arterial wall and cause atherosclerosis. You can ultimately see that all of these particles probably play an important role directly or indirectly to the atherosclerotic plaque.

I should say that the C-30 protein has been of recent recognition as a potentially important player in this atherosclerotic process and we’ll return to that in a moment.
When we think of postprandial hypertriglyceridemia, I think there’s an interesting study done by the Swedish group that is worth taking into consideration. What we’re looking at here in green is HDL cholesterol, we’re looking at LDL cholesterol in blue, and ultimately, we’re looking at remnant cholesterol in red.

Now, look at how this remnant cholesterol concentration relates to the triglyceride value. This is TGs around 90. This is TGs around 180. They keep going up based on around 100 or a little less than that. Multiple can. And ultimately, we see triglycerides go up and HDL cholesterol falls. We’ve talked about that. LDL tends to go up a little bit and then down a little bit when triglycerides are quite high. Let’s say they are above 500 milligrams per deciliter. But look at the cholesterol content in the remnant particles as triglycerides continue to increase.

These types of data support the idea that postprandial hypertriglyceridemia which relates in part to chylomicron and VLDL remnant formation may be an important consideration when we think about how triglycerides relate to the atherosclerotic process.

Let’s turn now to the genetics of hypertriglyceridemia. The historic definition of hypertriglyceridemia into two types of genetic traits was based on an autosomal inheritance and that was called familial combined hyperlipidemia or familiar hypertriglyceridemia. These autosomal dominant traits have been discarded now based on further genetic analysis coming from genome sequencing and beyond. Familial combined and familiar hypertriglyceridemia are not single genes, but polygenic traits reflecting the components of multiple genes that influence triglyceride levels. And a number of single nucleotide polymorphisms are snipped or polymorphisms have been identified that relate to hypertriglyceridemia.

Here’s just a simple example out of Rob Hegele’s lab in Ontario. Here are the genes that relate to triglyceride-rich lipoprotein metabolism including ApoA5, the glucokinase receptor lipoprotein lipase, the transcription factor TRIP-1, ANGPTL-3, and downstream all the way to ApoB. All of these have a variable significance in terms of the odds ratio of causing hypertriglyceridemia.

And two of the important ones are ApoA5 which is something we don’t routinely measure since it’s in such quantities. But the gene itself has been related strongly to hypertriglyceridemia. And of course, my favorite friend, lipoprotein lipase with an odds ratio of about 2.2. That’s a protein that my lab has been really interested in for a large number of years.

Now, if we add up the number of alleles that relate to patients with hypertriglyceridemia and we compare them with a control group. As you go from the odds ratio of being hypertriglyceridemia and hypertriglyceridemic patients versus control patients we’re seeing, as you look at the increasing ratios of being hypertriglyceridemia, the number of alleles that are informative alleles that have polymorphisms that relate to risk occur sequentially. And in the controls, those number of alleles are basically unfavorably modified into risk alleles when patients are hypertriglyceridemic.

This simply shows a case in point of risk alleles in an added fashion that relates to the prevalence of hypertriglyceridemia in data obtained from the Canadian Heart Health study.

Now, this is work from Kiran Musunuru and Sekar Kathiresan from -- . We see a very interesting genetic study about how lipids and lipoproteins relate to the risk for myocardial infarction. Do people with more LDL-raising alleles have higher MI risk? I’d say they do. And look at that P-value. It’s 10 to the
minus 10. We know that alleles that relate to LDL cholesterol values, ultimately, that genetic risk is highly predictable.

How about HDL raising alleles in terms of the protection of a lower risk for MI? Absolutely no genetic effect at all. It looks to me like the HDL story is more related to acquired levels of hypertriglyceridemia or other causes of low HDL cholesterol that are not predicted by who your mother and father are.

But look at this. Do people with more triglyceride-raising alleles have a higher risk? And that’s what we just talked about. And look at this. Ten to the minus six. It’s not 113% higher, but it’s still 54% higher. Does this suggest who your parents are and what genes you’ve inherited are important in relating triglycerides to coronary heart disease risk? Some people would conclude that they are.

But let’s look at this in a little more detail. Let’s look at the loss of function mutations and ApoC3. This is one of the apoproteins I mentioned a few slides ago that is bound to triglyceride-rich particles. And by the way, they are also found to be in HDL and found to be in LDL. But the majority of ApoC3 appears to be in triglyceride-rich particles.

This study which was ultimately published maybe now six or seven years ago looked at the triglyceride and HDL working group analysis of exome sequencing using data that was obtained through the National Heart, Lung, and Blood Institute. And it showed that loss of function mutations in ApoC3 relates to triglycerides in coronary disease. Remember, this is on triglyceride-rich particles.

Then a second paper followed similarly and shortly thereafter by the Swedish group. Loss of function mutations in ApoC3 and the risk of ischemic vascular disease. It’s also showing protection against atherosclerosis in patients with loss of function mutations of ApoC3.

And then, ultimately, the use of antisense inhibition of ApoC3 in patients with hypertriglyceridemia. Dan Gaudet from Canada and a large group of international geographic distribution showed if you block ApoC3 using antisense technology in patients with hypertriglyceridemia you lower triglycerides in a major way. This is suggested both in terms of genetic background and the ability to modify C3 and lower triglycerides. That maybe we’re looking at the causation of triglyceride-rich particles and triglycerides in terms of coronary heart disease at least.

Now, let’s take a look at VLDL in a little more detail in terms of the apolipoprotein content. All the VLDL have one molecule of ApoB. Some ApoB containing VLDL had ApoE, not all. But some ApoB containing VLDL have ApoC3 in addition to ApoB and some had ApoE and C3 and ApoE. VLDL comes in a wide variety of flavors and to say that one particle is causative is really difficult. But using the genetic data of C3, we can think that maybe C3 has a role to play in this atherosclerotic connection of triglyceride-rich particles, specifically VLDL and atherosclerosis.

Let’s look at the mechanism of the atherogenicity of C3 containing triglyceride-rich lipoproteins. First of all, C3 relates to the secretion of VLDL triglycerides in the insulin-resistant stage such as the metabolic syndrome in type 2 diabetes. ApoC3 also causes issues that relate to insulin sensitivity by increasing the concentration of protein kinase C beta which then results in lots of defects and insulin sensitivity. That’s true in peripheral tissues in addition to the liver itself.

The ApoC3 gene expression. This is a vicious cycle. It’s then created by some of the insulin resistance that’s caused by C3 itself. C3 increases insulin insensitivity resistance which is related to inflammation.
and that feeds back to increased ApoC3 gene expression. It relates to triglyceride-rich lipoprotein metabolism by defects in lipoprotein lipase. It relates to defects in the binding of ApoB lipoproteins to hepatic receptors and this is the remnant hypothesis in terms of how C3 influences that pathway. And it relates to the increased adherence of monocytes to the endothelium which is part of atherosclerotic plaque development.

And finally, it relates to the activation of monocytes ultimately to make them more active to control the atherosclerotic plaque development. And that’s through the TLR-2 mechanisms. Lots of reasons to think the C3 containing particle could be particularly atherogenic.

Now, we got to think also about all these secondary causes of hypertriglyceridemia which I alluded to earlier and that includes disease states and risk factors such as diabetes and insulin resistance. Not all obesity is insulin resistant, but most of it is and that’s where we think of metabolic syndrome.

Alcohol increases triglyceride production by the liver. Chronic kidney disease has a complex metabolic impact on triglyceride-rich particle metabolism, including catabolism and production. Nephrotic syndrome has an overproduction of VLDL and a defect in lipoprotein lipase. Hypothyroidism, most of the time, increases LDL cholesterol, but rarely and occasionally causes hypertriglyceridemia.

HIV including the many drugs that used to be used more commonly for HIV causes hypertriglyceridemia. People with hepatocellular disease. Notice I don’t say obstructive liver disease which is more cholesterol. They have hypertriglyceridemia and many inflammatory diseases. Systemic lupus erythematosus, rheumatoid arthritis, and beyond. Many of these are hypertriglyceridemia conditions.

And the drugs. Oral, not patch or vaginal or injectable estrogens. Bile-acid sequestrants, dose-related, antiviral regimens as I mentioned on this previous slide, second-generation phenothiazines, not selective beta-blockers, thiazides, loop diuretics, glucocorticoids, immunosuppressants, tamoxifen, and isotretinoin or vitamin A. Ultimately, we think of a plethora of causes of hypertriglyceridemia that are potentially in part correctable.

Now, I’m going to bring up a new concept about the new way we maybe should approach hypertriglyceridemia and that’s considering the use of ApoB. Remember, I mentioned every VLDL particle has ApoB included in its composition. And one ApoB molecule per particle. And I think assessing the potential atherogenic particle number very well because LDL also carries ApoB. We know most ApoB is in LDL, not in VLDL. But both of these particles carry ApoB-100 which is recognized by the LDL receptor and I think probably it’s at least related to strength and perhaps likely causative of atherosclerosis.

Now, Brian Ferrence who I mentioned earlier briefly published this study in JAMA in 2019 which I think is really a telling story. He evaluated over 650,000 participants including those that almost had 100,000 cases of coronary heart disease. And he analyzed a complex analysis using Mendelian randomization technology.

And what he looked at I put in this box here which is critically important. He looked at the association of LDL cholesterol, triglycerides, and ApoB with a risk of coronary heart disease in the same model. This again is Mendelian randomization considering all the genetic contributions. Look at the contribution of ApoB to atherosclerosis in terms of the relative P-value that relates to that association.
But look at LDL cholesterol in this analysis. We’re talking about 100,000 events. No statistically significant relationship or none of the triglycerides. But remember ApoB is carried in triglyceride-rich particles and carried in LDL. And ultimately, if you boil this down individually for triglycerides and ApoB without including the other lipid. Here, no triglycerides. Here, no LDL. ApoB carries all of the weight.

I’m not going to be overly opinionated here, but it’s the ApoB containing particles that don’t really matter that much maybe with its triglyceride and cholesterol content. But it’s ApoB that gets recognized downstream and leads to the atherosclerotic process. I’m thinking maybe it’s the entire ApoB enriched particle class that we can consider hypertriglyceridemia and perhaps triglycerides in LDL cholesterol may not be as causative. But it’s the ApoB ability to deliver cholesterol to the plaque that ultimately relates to atherosclerosis.

Now, this is one of my favorite slides. It’s almost 20 years old now, but I think it’s very telling. And I’m going to come back to this, particularly in one of the cases I’m going to be presenting to you. But when we think of triglycerides and atherosclerotic risk, coronary heart disease, or all forms of atherosclerotic cardiovascular disease should we be thinking of triglycerides or should we be thinking about non-HDL cholesterol? And I’m going to conclude right now that I think we should be thinking about non-HDL cholesterol.

Here’s what I want to show you as part of this presentation. Here’s the cholesterol concentration in millimoles. I hate that I can’t change the figure very easily, but millimoles of cholesterol. One millimole is about 40 milligrams per deciliter. This is 80, 120, 160, 200, and 240. You can see this is total cholesterol and here’s ApoB. And now, we’re looking at milligrams per deciliter, units we recognize really well.

All these P-values are significant. If we look at the relationship of ApoB to total cholesterol, ApoB to LDL, cholesterol to HDL cholesterol, and non-HDL cholesterol. But here’s what I want to point out to you, ApoB to non-HDL cholesterol. Now, here’s what I did in the clinic for years and again, these are not guidelines established, but it’s what I’ve used and I believe this is the way we should think anew in terms of how to relate triglycerides and non-HDL cholesterol to ApoB in atherosclerotic risk.

We look at the 95th percentile of ApoB around any given level of non-HDL cholesterol. Here’s non-HDL cholesterol of five which would be a value of about 190 milligrams per deciliter in which would be correlated with maybe an LDL if we had normal triglycerides in HDL of around let’s say 150 or 160. Look at this variation in ApoB in someone who has the same level of non-HDL cholesterol.

And by the way, you can do the same thing with LDL down here. I didn’t draw the graph for that.

When I see a patient with triglycerides of let’s say 300 or 400, their non-HDL cholesterol is elevated based on their non-HDL cholesterol, and I get an ApoB of 150 or I get an ApoB of 90. My approach to these patients may be very different based on how I think their triglycerides are related to coronary heart disease. Again, this is not guideline stuff, but it’s related very much to the way I’ve practiced lipid-related medicine and it’s something you should think about when to measure ApoB. We don’t need to measure ApoB in everyone because the relationship between LDL and atherosclerosis is quite convincing. Although, what I pointed out to you from Brian Ferrence’s analysis is that may be more ApoB related than LDL.
And Allan Sniderman for years has been an advocate of why aren’t we replacing lipids with apoproteins or lipoproteins such as ApoB and ApoA1. And I’m not condoning that opinion only because we missed triglycerides at 450, 500, 800, or 1000. I’m don’t think we’re ready right now for this, but I think this is a slide that points out maybe the utility of using ApoB in patients whose non-HDL cholesterols are elevated because their triglycerides are elevated.

Now, triglycerides versus non-HDL cholesterol. If you plot all of the drug-related trials, statins, fibrates, niacin, or omega-3 fatty acids through 2019, ultimately, the relative risk ratio continues to be further modified as ultimately non-HDL cholesterol is reduced shown here on the axis. And triglycerides are not shown. But you can look at the triglyceride-lowering trials. REDUCE-IT is one. The fibrate trial such as ACCORD. You can look at all the trials that have been done with various drugs. JELIS with omega-3s and the statin trials are big boxes because there are so many of them with this degree of non-HDL cholesterol lowering.

I’m going to point out this. Maybe non-HDL cholesterol which is suggested by the ACC and AHA Guidelines is a better outcome to be paying attention to than LDL cholesterol.

Again, for one millimolar of cholesterol that’s around 39 milligrams per deciliter. That amount of reduction in non-HDL is a 23% risk reduction for people in non-stain trials and a 20% reduction in those people on the statin-based trials.

Management of Hypertriglyceridemia

DR. ECKEL: Now, onto the third learning objective. It’s to evaluate the various strategies for triglyceride management and that’s to address patients with moderate hypertriglyceridemia and patients with severe hypertriglyceridemia.

Let’s begin with lifestyle. Let’s think a little bit about a heart-healthy lifestyle which is really a cancer-healthy lifestyle and a diabetes-related lifestyle. And we’re basically related to dietary patterns here, a Mediterranean style diet or a Dash diet. Lots of fruits and vegetables, lots of whole grains, and restriction of saturated fats and trans fats which are pretty much out of the diet now in terms of packaged foods.

This is a type of diet that is enriched with lean poultry and fish and legumes, et cetera. This is a diet that lowers LDL. It lowers blood pressure. It lowers triglycerides modestly. But it’s a good diet. And also, it has glycemic lowering capabilities. In fact, simple sugars are restricted. I’m going to put it as a sub-note when implemented additional simple sugar carbohydrate restriction may not be so necessary. That’s because when it’s implemented there’s not a lot of room for extra calories when you own a Mediterranean style or a Dash dietary pattern.

Regular physical activity defined by guidelines now is three to four sessions a week, lasting on average 40 minutes per session and that’s a moderately vigorous physical activity. Or it can be a higher intensity physical activity which could be less. But nevertheless, I think the average prescription for physical activity should relate to three to four sessions a week at a minimum with a moderate activity of at least 40 minutes in duration.
And then weight loss. And typically, 10% is best for lipids including triglycerides, and 5% is not much of a hit here, but you do get a little bit. But the more weight loss you use and sustain that weight reduction the more triglyceride-lowering you get. That’s going to be recommended for a lot of our patients with obesity, metabolic syndrome, type 2 diabetes, and beyond.

Now, here’s the drug effect. Fibrates are between 20 and 45%. Niacin. By the way, nicotinic acid or niacin I think is pretty much a drug we need to leave on the shelf now and I’ll come back to that a little bit when we talk about HDL to follow.

The omega-3 fatty acids. You need to use a prescription type omega-3 preparation. The over-the-counters are not recommended. They’re not guideline-based. There’s no FDA indication. And here we’re looking at between 15 and 35% lowering on the average.

Statins are 0 to 35%. Low-end statins have minimal or no effect and high-intensity statins such as rosvastatin and atorvastatin moderate to a high dose can be up to a 35 or even 40% lowering in some patients. This is a drug that we should consider in patients who are going to be on statins anyway to dose escalate to try to get that additional triglyceride-lowering effect if we feel it’s indicated.

Now, I hate to bore you, but I’m going to review this brief of the major fibrate cardiovascular disease outcome trials in terms of the primary outcome. The only two that came out favorably were the Helsinki Heart Study and the VA HIT study. Let me define these a little bit more in detail. The Helsinki Heart study was carried in patients with LDL cholesterol levels around 190 milligrams per deciliter. A fairly good sample size.

The outcome was fatal or nonfatal MI or cardiac death. There was a 34% reduction, but that reduction did not relate to triglyceride lowering. It is related to the benefit modest effect of HDL and the effect on LDL cholesterol-lowering which you get with a fibrate when LDL cholesterol is 190. You don’t typically see that with a fibrate when LDL cholesterol is 110 or 120.

The VA HIT study was men only and was carried out in the VA in 1999. All men with low HDL cholesterol and the primary outcome was nonfatal MI or cardiac death. This was a 22% reduction and this study is worth acknowledging because of the nature of the study. Triglycerides were not that high. I believe they were in the 160 to 17 range, but the HDL cholesterol was all below 40 in these men in the VA HIT study. That study has never been reproduced and now that women have been added to the studies we don’t see that effect in either men or women in terms of the primary outcome.

Then there’s a series of trials. BIP with bezafibrate, LEADER with bezafibrate, FIELD with fenofibrate. This was the initial LEADER trial. This is not the more recent LEADER trial with liraglutide. ACCORD is simvastatin plus fenofibrate. The comparator here was simvastatin and that was part of the study in type 2 diabetes. And the ACCORDION trial with simvastatin and fenofibrate compared to simvastatin. The primary outcomes differ a bit from each other, but all of these trials with a primary outcome were showing variability of reduction of 4% of the 9.4%. All nonsignificant.

Why the VA HIT study was successful with gemfibrozil? We can explain this through LDL lowering. And by the way, the VA HIT study did not show the amount of triglyceride reduction related to the benefit. In none of these trials was the amount of triglyceride-lowering with a fibrate drug statistically significant based on the primary outcome nor did it relate to what was statistically significant. But none of them related to triglyceride reduction.
Now, hazard ratios for the primary outcome and prespecified subgroups. I’m just going to show one trial here and Barney Elam from Memphis shared these data in 2016. This is a hazard ratio for the primary outcome in prespecified subgroups. Here, we’re looking at HDLs that are quite low versus above 41, triglycerides less than 129 up to 203 and 204, dyslipidemia defined as not present, or triglycerides above 204, HDLs less than 34, and A1cs.

Here we show, like many other trials, A1cs did not predict the outcome from a fibrate intervention. But here in this subgroup analysis which was prespecified, it looked at the group above 204 and HDL cholesterol under 34. And there was a statistically significant reduction of 27%. Maybe this is a hint of where we need to go. We need to stratify patients into this dyslipidemic group as defined as triglycerides above 200 and HDLs below 35 or around those numbers to see whether or not the fibrate may be better.

There’s that analysis that I think deserves some attention.

Now, there’s such a trial going to be happening and I’m part of the Scientific Advisory Committee for this trial. It’s called PROMINENT which is pemafibrate to reduce cardiovascular disease outcomes by reducing triglycerides in patients with diabetes. Look what they have to do to come up with a trial name. You’ve got to play games of all the characters in this particular algorithm here and ultimately, come up with PROMINENT.

Anyway, pemafibrate is a fibrate drug, but it’s in a class called SPARM-alpha which is defined as having very high PPAR-alpha selectivity. Now, you may recall drugs like pioglitazone that are PPAR-gamma dependent which really have a major effect on insulin sensitivity. Whereas PPAR-alpha selectivity relates to its effects on lipid metabolism predominantly and that’s inducing triglyceride hydrolysis in the generation of free fatty acids.

The SPARM-alpha trial is related to this very high PPAR-alpha selectivity beyond fenofibrate, gemfibrozil, and bezafibrate.

The primary objective of this study is to determine whether pemafibrate administered twice a day will delay the time to the first occurrence of any component of the clinical composite endpoint of nonfatal myocardial infarction, nonfatal ischemic stroke, hospitalization for unstable angina requiring unplanned coronary revascularization, or CVD death. And the condition or disease necessary is type 2 diabetes with dyslipidemia defined as I previously described. Elevated triglycerides with an HDL cholesterol of less than 35 for men and less than 40 for women.

Here’s what that trial design looks like. This has now enrolled 10,000 participants in 24 countries around the world. There is a placebo run-in to make sure there’s no adverse effect to verify the LDL is under control and the LDL under control should be under 70 or people on existing therapy or less than 100 for those who are statin intolerant. A third of these patients, by the way, is going to be primary prevention, meaning no previous atherosclerotic cardiovascular disease events and two-thirds will be in those people with existing atherosclerotic cardiovascular disease events.

Placebo b.i.d., pemafibrate 0.2 b.i.d., and a series of these over months to years to ultimately look at the expected outcome in about five years. We’re thinking about the earliest may be released in early or mid-2024 based on this design.
I’m going to turn a little bit to the JELIS study just in terms of the relationship between this triglyceride-lowering benefit in terms of the outcome. A total population was studied and those with primary prevention were separated in this analysis to look at the outcome. And basically, the total population benefit was explained entirely by the secondary prevention population. And this group of patients, some 18,000 plus, with total cholesterol greater than 250 and the EPA dose alone. This is eicosapentaenoic acid only at 1.8 grams a day.

Here’s the benefit that was carried out over five years in patients with a relatively low pravastatin dose who were treated for existing disease and secondary prevention. And ultimately, it’s an outcome that looked like it was beneficial with a dose of EPA only.

This trial, JELIS, is one in addition to other trials that I’ve reported to you earlier that shows the benefit of the high triglyceride patient who also has lower levels of HDL cholesterol in predicting risk. In JELIS, looking at the subpopulation of cardiovascular disease risk reduction we’re looking at now a 53% risk reduction in patients who are designed to have a maximum benefit from intervention with triglyceride lowering. Again, the amount of triglyceride-lowering in this subgroup analysis did not relate to the benefit to follow.

Now, let’s look at some more recent trials that really have, to some extent, duplicated the effective EPA on cardiovascular disease outcomes. The REDUCE-IT trial, which I’ll report in some detail, had 8000 plus patients using a primary outcome of a 5-point MACE. And people, in fact, had triglyceride levels at baseline from 135 to 500 on the maximum tolerated statin dose, unlike the JELIS trial. The STRENGTH trial also had patients on maximum tolerated statin doses with triglycerides ranging from 180 to 500. The difference between these two trials is the type of omega-3 fatty acids that were used.

Here icosapent ethyl which is effectively EPA was the drug of choice or the nutraceutical of choice. Whereas STRENGTH used a combination of EPA and DHA in the form of carboxylic fatty acids. All patients in both trials were on statin therapy.

Here’s the REDUCE-IT trial. The lead offering is Deepak Bhatt and Christy Valentine, one of our co-chairs at the Cardiometabolic Health Congress and one of our participants in the certificate program which you may have already heard from was a co-author on this trial.

Again, patient size. All were at high risk for cardiovascular disease events or having atherosclerosis and those people with established heart disease are well defined or have some form of cardiovascular disease. And people at high risk were defined as having diabetes greater than the age of 15 with at least one risk factor or more for CVD including hypertension and beyond. They were randomized one to one stable statin plus placebo or 4 grams a day of Vascepa or icosapent ethyl or EPA. The primary outcome is the 5-point MACE I just alluded to before.

Here’s the primary endpoint. If you will, a substantial 25% reduction over the period of study and the key secondary endpoint which actually related to I think a 4-point MACE rather than a 3-point MACE. Again, highly significantly reduced at 26%.

Here we’re looking at a major impact of EPA alone versus placebo on -. And the interesting impact of using hierarchical testing is the impact on a series of additional major CVD events that must depend on the initial outcome being positive. It looked at the primary and secondary composite which I’ve already shown you. CVD death or nonfatal MI, fatal and nonfatal MI. You can read these down the list.
The only thing that was not impacted was all-cause mortality with a trend towards a reduction in all-cause mortality. And that may be simply related to the duration of the study. Keep in mind when the primary outcome is achieved at the affected and predicted number of events then ultimately other outcomes may not be impacted because of the duration of the study. And I think that’s true for the REDUCE-IT trial as it has been for many other cardiovascular disease outcomes using statins and other drugs.

Now, importantly, the CVD event did not relate to the amount of triglyceride-lowering using icosapent ethyl or that form of EPA or JELIS or any of the fibrate trials that precluded this.

And if we look at subsequent events in terms of not only the first event which was really powered by the analysis upfront, but now we’re looking at additional events and looking at the details in patients treated with drug or nutraceutical icosapent ethyl versus placebo.

And we’re looking at greater than four events shown at the top. Three events, two events, and first events only. We’re looking at a substantial reduction in the total number of events over the interval of observation. This is an incredibly beneficial effect that relates substantially here using a hazard ratio anywhere up to a 48% reduction in those people who had four or more events.

Now, what Preston Mason and I’ve done recently is compare these three trials, JELIS, REDUCE-IT, and STRENGTH, and look at the formulations and the population to be studied, baseline median triglycerides, baseline levels of EPA, achieved EPA levels, increase in EPA percent increase and this relates to the basal, of course. Triglyceride lowering effect, and the primary endpoint here. And here we’re looking at the hazard ratio of the primary endpoint looking at JELIS 0.81, a 19% reduction. Again, REDUCE-IT, we just reviewed this. It’s a 25% risk reduction. And STRENGTH failed to have a statistically significant benefit of the combined omega-3s of DHA plus EPA.

Why is that? Well, one thing we think might think about is the EPA levels. JELIS already started with a high EPA level whereas REDUCE-IT started with a much lower level as did STRENGTH. But the EPA dose was higher with the IPE form of EPA. The achieve level here.

Ultimately, it reached the achievement level or close to it that was present in JELIS. Whereas the achieve level here in fact was only about two-thirds of that achieved in the REDUCE-IT trial. There may be some thought that the level achieved may be an important part of why EPA alone works and DHA doesn’t. But we’ve analyzed this further in thinking about mechanistic insights from REDUCE-IT strengthening the case against triglyceride-lowering as a strategy for cardiovascular disease risk reduction.

And here’s the clinical significance of this paper we have published just recently in the American Journal of Medicine. Elevated triglycerides we think are associated with increased risk. However, the current triglyceride-lowering therapies are ineffective in reducing such risk. Icosapent ethyl which is a highly purified EPA in REDUCE-IT was shown to reduce events by 25% and not associated with triglyceride lowering. Icosapent ethyl or EPA appears to have broad pleiotropic effects associated with on-treatment levels of the EPA achieved.

And the evidence against triglyceride-lowering and reducing CVD risk should guide other therapeutic strategies to follow. And here are some of our thoughts. Preston Mason is a basic biochemist-
biophysicist and I’m a lipid guy who’s done a fair amount of basic science, but I’m going to give credit to Preston Mason for most of the thinking behind this.

But the idea is most of the effect here is at the endothelial cell level and that includes cholesterol crystallization, antioxidant activity, and ultimately effects on plaque generation and disease progression. Some of this may relate to inflammation. Whereas DHA is maybe not harmful, but when EPA levels are not achieved some of the effects of DHA membrane composition and function may be modified.

By the way, DHA is great for the brain and I think when you should think of omega-3 fatty acids as a therapeutic strategy or at least a preventive strategy for Alzheimer’s and other neurodegenerative disorders. And when we think about neural development, DHA is very important in maternal feeding and also in early infant feeding to relate to some of the retinal development that occurs in the early phases of development. We’re not excluding DHA and not saying it’s bad, but the membrane compositional changes relate more to the activities of the endothelial cell that may provide a unique value in terms of how EPA biophysically impacts biology downstream that could relate to the atherosclerotic process to follow.

If we’re thinking about the atheroprotective effects of EPA and its endothelial function, nitric oxide bioavailability, lipid membrane stability, vasodilatation, and free radical scavenging. I mentioned some of these at least on the previous slide. Ultimately, it relates to atherosclerotic plaque development and plaque stability to follow.

Well, when EPA levels are low, ultimately, plaque progression continues with endothelial dysfunction, oxidative stress, inflammation, plaque growth, and unstable plaque to follow. This is just conceptual and published in our recent paper and it might be a worthwhile read just to get an understanding of whether triglycerides themselves cause or they’re simply associated in values of ultimately lowering, not only ApoB containing lipoproteins with statins but also thinking about why EPA alone may be beneficial if adequate EPA levels are achieved.

**New Kids on the Block for Triglyceride Lowering**

There are some new kids on the block for triglyceride-lowering that I think in the upcoming years you maybe need to pay attention to. I mentioned ApoC3 and its pro efforts and equalities before both in lipoprotein metabolism, insulin resistance, and beyond. And volanesorsen is a drug that’s now being reconsidered by the FDA in the treatment of severe hypertriglyceridemia which we’ll come to in a second. But also, in patients that have more modest hypertriglyceridemia. There’s a dose-related and time-related lowering of triglycerides that are very expected and may be available for patients with moderate degrees of hypertriglyceridemia.

Now, I’m going to turn to angioptietin-like proteins for a moment that is genetically present and related to risk. And I’m not going to show you the papers that have come out there, but that relate to angiopoiitin-like proteins as a target for triglyceride lowering. Angioptietins 3, 4, and 8 are important modulators of lipid metabolism. Angiopoiitin-3 is a circulating protein synthesized in the liver that modulates lipid and lipoprotein metabolism and has other pleiotropic functions that relate to atherosclerosis.

And the gene coding for this is specifically expressed in hepatocytes and also its expression is regulated by LXR which is an important receptor that though binding to proteins it recognizes that receptor related
to the atherosclerotic plaque. It undergoes cleavage which is mediated by PCSK3, not 9, and PCSK-6, not 9, and phosphorylation.

And the effect of angiopoietin-3 on lipoprotein lipase activity is more pronounced postprandially due to its interaction with angiopoietin-8. And I can just say in my laboratory now we use angiopoietin-3 as a way to knock out LPL activity both in cell culture systems and in animals to look at the effect of LPL on lipid and lipoprotein metabolism. It’s a very important inhibitor of lipoprotein lipase.

Here are weekly injections for six weeks of various doses of anti-angiopoietin-3. This is an antisense technology just like that used for lowering triglycerides with anti-ApoC3. And here we’re seeing ultimately weekly injections for six weeks and then no injections at all for up to almost 127 days. You have to do those calculations. We’re talking about maybe up to four or five months.

Here’s the effect on triglycerides. Here’s the effect on C3 levels. The C3 levels parallel the effect on triglycerides with a bit of warning when you get out to 127 or 130 days. But nevertheless, the idea that injection for six weeks could last for up to four or five months really gives us indications that we may be looking at something very promising going forward.

And here’s ultimately a modified antisense technology using antisense angiopoietin-3, not an antibody, but another antisense technology using the galactosamine modification of this antisense technology. This is vupanorsen and ultimately we’re looking at an administration and dose-related response over a period of up to four weeks here. Ultimately, this technology is there ready for primetime once the FDA approves it through phase II and phase III clinical trials for human application.

Then there’s an antibody, evinacumab which as a percent is median for Q1 through Q3 change in plasma triglycerides. This is a complicated slide, but these injections were carried out weekly every two to four weeks. And here are the doses shown over here where they’re given subcutaneously or intravenously. With higher doses shown down here ultimately you get a greater effect which is shown over a longer period of time. We’re looking at study days down here out to three months.

This is another potential strategy using an antibody rather than antisense technology that’s going to be effective in modifying triglyceride levels over a longer period of time.

Management of Severe Hypertriglyceridemia

Now, we’re going to turn to severe hypertriglyceridemia shown here by these plasmas from a patient with normal triglycerides or a patient whose triglycerides are over several thousand milligrams per deciliter. Now, with severe hypertriglyceridemia, we think of familial forms and all etiologies do not require secondary disorders. This is simply a genetic modification that I’m going to show down here.

Ultimately, this degree of hypertriglyceridemia can be associated with cutaneous eruptive xanthomas typically on the extensive surfaces of the upper and lower extremities and on the gluteal region. Lipemia retinalis is shown as a white vasculature when you do a retinal exam. And ultimately, it’s a risk for pancreatitis.

Basically, patients with familial chylomicronemia do not get coronary heart disease. That’s because the particles that are retained in the plasma are chylomicrons. Those are big particles that don’t get metabolized adequately by LPL and ultimately, they are no proatherogenic.
Again, the eruptive xanthomas are shown here and lipemia retinalis here.

LPL deficiently, at least in most populations, is rare. It’s one in a million that’s a homozygous deficiency. The heterozygous condition can be one of those genes that’s associated with genetic causes of moderate hypertriglyceridemia, but you need to be homozygous to have severe hypertriglyceridemia.

In the French-Canadians, there’s a much more added mixture and ultimately, 1 in 40,000 as it is in South Africa and a much higher prevalence in the - - also.

I mentioned earlier ApoC2 is the activator of lipoprotein lipase and patients with homozygous C2 deficiency are also chylomicronemic, but they tend to show up a little bit later and are less pronounced in terms of the extent of their hypertriglyceridemia than people with LPL deficiency.

LMF-1 deficiency is a defect in the transport protein that transports LPL to the endothelium. And the GPI-HDL binding protein binds LPL to the capillary endothelium. All of these defects relate to LPL but cause hypertriglyceridemia as is LPL deficiency in its own right.

Now, the most common cause of hypertriglyceridemia and is really important to stress. It’s historic type 5 hyperlipoproteinemia which are genetic forms of hypertriglyceridemia due to VLDL. And then acquired secondary factors that are superimposed on multilin e allelic mutations in genes that are related to triglycerides and acquired secondary factors that cause hypertriglyceridemia.

Let’s look at this biologically and I think I’m going to spend a few minutes on this slide because it’s so important to understand. Remember, most patients with severe hypertriglyceridemia relate to this biology, not LPL deficiency that’s due to homozygous mutations in the LPL gene.

If we look at patients who produce a normal amount of VLDL and their triglyceride levels are around 100 or so. Here are 90 milligrams per deciliter. And we’re looking at a sink to use as a metaphor. A sink with water up to a certain level. Triglyceride removal, because the sink is only partly full with water, is not very limiting. That needs the input of water from above. It equals the outflow. The input of triglycerides from the liver relates to a normal amount of lipoprotein lipase.

KM, by the way. I’m going to take you back to basic biochemistry. VMAX relates to the total amount of enzyme and KM is the substrate concentration. Here are triglycerides at which half of VMAX is saturated. When we get saturation kinetics we’re looking at whole different biology. But in this degree of hypertriglyceridemia or normal triglyceride levels, the removal of triglycerides equals the production rate. We’re not saturated.

But when VLDL is produced excessively then we reach a level of enzyme saturation and ultimately now the chylomicrons start to accumulate in the plasma. When we get levels up around 500 but then above 1000 for sure these chylomicrons are not removed adequately. But the lipoprotein lipase enzyme is saturated and the sink is now full.

As long as the sink is turned on, ultimately, triglyceride removal is saturated and now water goes onto the floor. This is the example that Allan Tate and I pointed out Chait pointed out in our analyst paper in 2019. It’s the metaphor I’ve used with patients for many years now. Let’s think about a sink with water and when your triglycerides are normal we don’t have any problem getting triglycerides too elevated. But when the sink is full, your dietary fat relates to how full the sink is. What do we have to do to modify the risk for pancreatitis and get rid of these chylomicrons and get your triglyceride levels back
where LPL is more functional and down here at a level which creates normal or just modestly elevated triglyceride levels? We need to get dietary fat out of there.

Here’s our dietary treatment of severe hypertriglyceridemia. In all of the patients I’ve seen for decades when their triglycerides are above 1000, I reduce their dietary fat to less than 5% calories. I need a nutritionist who works very closely with me here and I need to make sure the patient understands that this is not a long-term dietary paradigm. This is going to be used until we get your triglycerides down to where the sink now no longer overflowing onto the floor. And of course, no alcohol during this period of fat restriction.

The question is do you discontinue all triglyceride-lowering drugs at this point excluding statins. The reason I think maybe discontinuing them has two reasons. The drugs don’t really work when the triglyceride levels are this high and that is true of the triglyceride-lowering of the statins when triglycerides are 2000 and 3000. But it’s also by the fact that the patient now understands how important fat restriction is to get rid of this very high triglyceride level in plasma.

Now, once the fat is restricted adequately, ultimately, we predict we lose about 25% of our triglycerides daily in a setting of saturation kinetics. Until triglycerides get under at least 1250 or 1000 I can predict to the patient as long as you’re following the dietary paradigm we’ve recommended I can predict how many days it’s going to take to get your triglycerides down to a reasonable level. In the clinic, I check triglycerides every three days until the triglycerides are down below 1000.

Now, the next steps. I restart the drugs then when triglycerides are below 1000. And by the way, then you can see triglycerides go from 900 to 450 to 500 three days later and if we add a second drug it’s often down into the 200 to 250 range. But those drugs aren’t working when triglycerides are above 1000.

And remember what I said. I think the reason I stop drugs is not to cause harm, but because now when we introduce them to the patient and they become better they’re capable of understanding why their triglyceride levels have been so elevated. That’s just a thought. That’s not guidelines. That’s an echo opine. But nevertheless, it’s worked very well for me keeping people out of the hospital and in the outpatient clinic for years and years.

And if the triglycerides don’t reach 1000 the person is either not following the guide or they maybe have a rare form of genetic hypertriglyceridemia. And if we can’t get the triglycerides under 1000 as an outpatient, hopefully, you can get a third-party payment coverage for hospitalization in controlling it in the hospital. And having a general clinical research center for many years in Colorado we did that I think in a handful of patients over the long time that I’ve been at that university. I would say less than 10 times or maybe 5 or 6 times over the years. And proven that in the hospital we can get triglycerides to be reduced with the appropriate dietary management.

Now, once the patients get their triglycerides down into this moderate range I increase the dietary fat up to the current recommendation of 20 to 35% of calories. And ultimately, if your triglycerides go up when you do this type of thing then decrease the carbohydrates and increase the mono and polyunsaturated fats. Because when you increase the fat ultimately you should affect the triglycerides and fall, but if the triglycerides go up if you’re on 20% then maybe carbohydrate restriction works. But in general, this type of dietary approach has worked very well in my experience.
And I think when TGs get under 400 people can tolerate a little bit of alcohol. If they’re closer to 400 you might want to wait on that a bit. Fiber is good at 25 grams daily. Sucrose in moderation. And I think we then need to reach what’s the bottom line.

When we lower triglycerides to less than 500 milligrams per deciliter pancreatitis risk is reduced dramatically. We want to take all our patients with hypertriglyceridemia initially to make sure their LDL cholesterol is being reduced consistent with guidelines.

I think we need to consider ApoB as an indicator of CVD risk in patients with an LDL of less than 100 to 130 whose triglycerides are above 150. I think ApoB can be very helpful. And remember, almost a two-fold elevation in ApoB at any given level of non-HDL cholesterol that can help you know which patients need more aggressive management, not necessarily in triglycerides management, but maybe in ApoB lowering therapy that relates to drugs that lower ApoB more so than fibrates or omega-3s.

Patients with fasting TGs above 200 plus low HDLs. I think they should consider a fibrate. I would be more likely to use EPA. And as noted in the last point, EPA in most high-risk CVD patients seems reasonable. People doubt that study a little bit because the placebo was mineral oil and ultimately, the REDUCE-IT. And it was corn oil in the STRENGTH trial. But the FDA’s given an indication for this and if you control for the placebo you still have a pretty dramatic lowering of cardiovascular disease risk.

I think it relates to the EPA level and I think in consideration of which fatty acid to use I think EPA would be the drug of choice. And whether it should be done in all high-risk patients I think is open to your own discretion of the literature, but there is an FDA indication for that there now.

HDL-C Science and Management

Now, let’s think about summarizing the last objective here in this presentation. It’s to look at the HDL science and related management for patients with low HDL levels.

We’ve known for a long time now and this is just one diagram relating total cholesterol and HDL to incidence over four years in men and women on primary prevention. And this is just showing how HDL is a strong predictor for risk, particularly low levels being important in relationship to total cholesterol. Though once HDL cholesterol gets into a low range here the total cholesterol ultimately is also important. We consider both. This is just one cartoon. There are many like this that I could have shown you.

First, let’s think about the acquired causes of low HDL. As I mentioned before, genetic causes of low or high HDL cholesterol do not seem to be important in predicting risk for at least coronary heart disease. Insulin resistance. We’ve covered hypertriglyceridemia at the very inception of this presentation. Obesity, by the way. The US by far. What the most important lipid abnormality in patients with obesity is not hypertriglyceridemic. It’s a low HDL cholesterol. If you’re asked that question in a quiz going forward make sure you remember a low HDL cholesterol is the most common lipid abnormality in people with obesity.
Cigarette smokers have low HDL cholesterols. Anabolic steroids. I’ve seen a couple of people who take anabolic steroids over the counter and the HDL cholesterols are in the single-digit range. I remember one guy had five or six milligrams per deciliter. That’s a question you should ask your patients.

Drugs, HIV, proteasome inhibitors, sirolimus, beta-blockers, IL-2, proteinuria. Proteinuria is a major cause of loss of HDL in the urine and makes HDLs quite low. And most patients with proteinuria also have elevations in triglycerides and total cholesterol and LDL cholesterol. Critical illness lowers HDL and maybe a predictor as total cholesterol is a bad outcome in critical illnesses. Paraproteinemia is occasionally associated with lower levels of HDL.

With obstructive liver disease, the HDL goes up, and also, the LDL total cholesterol can go up a lot in people with primary biliary cirrhosis or other forms of obstructive liver disease including gallstones, et cetera. The disappearing HDL syndrome is quite rare but related to a few drugs that are associated with this so-called where is HDL. Where has it gone? And I don’t think that biology is well studied because of the rarity of that syndrome.

Now, there’s a paradox with HDL cholesterol levels. There are CETP deficient Japanese families with HDL levels that can be very high and heterozygous and there may be an increase in HDL. That hasn’t been followed up with too much recently because of where the HDL story has gone.

ApoA1 Milano have low levels of HDL and they live into their 90s, et cetera, and they have very low HDL risk. That’s something else we don’t understand, although A1 is made, it’s just cleared very rapidly. The idea you have some HDL being made, but it’s just cleared much more rapidly may be a reason why those patients don’t have more atherosclerotic risk.

Tangier disease. ABCA1 deficiency is a rare genetic disease. I’ve seen one case in my life. Those patients don’t typically have much atherosclerosis, although this is a rare disease.

Genetically low HDL cholesterol. This occurs in Turkey and China. This is a hepatic triglyceride gene mutation and when these people relocate to an urban environment their risk may go up and that may relate to the low levels of HDL. But again, a rare disorder is rarely seen. We don’t typically see that where we operate within.

Type 1 diabetes is an interesting paradox. Patients with type 1 diabetes have higher levels of HDL cholesterol than the average, but we certainly know that patients with type 1 diabetes have a higher risk of not only coronary heart disease but all forms of cardiovascular disease. And many patients without low HDL cholesterol have coronary heart disease.

We know the HDL paradox is worth paying attention to and now that the HDL story has evolved as I’m going to outline how I think this becomes a less important lipoprotein for us to think about clinically in terms of modifying it favorably.

Part of that reason is that dysfunctional HDL may be harmful and that doesn’t relate to levels. Increased levels of circulating HDL don’t necessarily decrease the risk for coronary heart disease or mortality. And some of that may relate to the HDL sometimes acting as an anti- versus a proinflammatory molecule depending on the context and the environment it exists within.
And based on a number of recent studies, it appears that the anti and pro-inflammatory nature of HDL may be a more sensitive indicator of the presence or absence of atherosclerosis than HDL cholesterol levels themselves. This is something that’s evolving biology and doesn’t reach clinical levels quite yet.

Just like VLDL and other lipoproteins, HDL comes in a wide variety of flavors, including A1-only HDL, A1/A2 HDL, and ApoE containing HDL. And by the way, HDL starts as a discoidal disk that has no Apo1 on it, but becomes spherical by the action of LCAT and then grabs A1 and becomes the series of particles to follow.

And as I pointed out earlier, HDL-2 are the larger particles whereas HDL-3C is the smallest which are derived as the ultimate metabolism of these smaller forms of HDL and the transfer of unesterified cholesterol and phospholipids through LPL to make these particles larger. Again, lots of flavors of HDL and all particles may all differ for a wide variety of reasons.

This is the HDL proteome. The HDL protein content relates to a wide variety of biological features. Here’s the lipid metabolism. Look at all these lipid-related genes that bind to HDL that relate to lipid metabolism. Large numbers here can modify lipid metabolism up and downstream that relate to its synthesis and metabolism.

Protease inhibitors are bound to HDL particles which also may relate to the acute phase response. Notice the bidirectional areas here. And also, complement regulation. The complement pathway can also bidirectionally impact a few of the proteins that relate to lipid metabolism through these complement proteins shown here.

This proteome for HDL is complex and doesn’t just say that HDL carries cholesterol and lowers are harmful and higher levels are good. It’s much more biologically complex and difficult to understand, particularly as we look at the clinical trials.

And here’s the potential anti-atherogenic actions of HDL. It can cause vasodilatation. It can affect platelet thrombosis and have antithrombotic effects. It actually is anti-infectious and causes reverse cholesterol transport which we’re going to look at in a moment. It relates to endothelial repair. It has antiapoptotic qualities, antioxidative activities, and anti-inflammatory activities. Look at all of this and this relates to HDL in these pleiotropic forms in which it occurs. No wonder we have trouble understanding HDL.

Here’s the common mechanism by which people think HDL is favorable. Nascent HDL is formed, as I just mentioned, as a nascent disk that acquires ApoA1 through a reverse cholesterol transport process in which we’ll look at in more detail. LCAT esterification or cholesteryl ester core which is the mature form of HDL that’s ultimately mostly taken up and degraded by the liver. And the half-life of HDL is in the form of days. Three or four days to turn this pool over.

Now, here’s the macrophage which shows a little bit more detail. The LXR pathway which I mentioned earlier ultimately stimulates the production of these transport proteins by which HDL binds and ultimately promotes the transport of cholesteryl ester from these cholesterol-enriched macrophages onto HDL.
What happens then? Once the HDL is loaded with cholesterol it’s involved in transferring that HDL ultimately back to the VLDL and LDL to the liver or it actually transports that cholesterol, takes it up, and delivers it directly to the liver.

Now, ultimately, when CETP is inhibited which relates to the transport of cholesterol from HDL to VLDL and LDL. But HDL levels go up to a major extent and it’s not because the transport of HDL directly into the liver is modified. By the way, the liver has a way of excreting this cholesterol in bile. Ultimately, the liver dumps the cholesterol and bile and it’s not proatherogenic once it reaches the liver.

But once this pathway of CETP is blocked, then all of the delivery occurs to the liver directly and the HDL levels and plasma go up a lot. This pathway probably contributes to the majority of reverse cholesterol transport, not the direct pathway through SRB-1, the hepatic receptor for HDL. As I said, A1 levels go up, HDL particle numbers go up, but ultimately it may not be that this pathway is the process by which HDL works and that’s why a lot of the drug trials with CETP inhibitors have failed. I’m going to review this in a moment.

But ultimately, the Dallas group has looked at maybe the cholesterol efflux capacity of HDLs is where we should be looking, not the level. And ultimately, these are studies from coronary artery disease patients obtained through the cohort that exists at UT Southwestern Medical School where they’ve looked at the risk factors for atherosclerotic cardiovascular disease related to diabetes, hypertension, smoking, LDL cholesterol, HDL cholesterol, and efflux capacity.

The HDL levels were somewhat protected, but the coefficient of variation crossed one, but the efflux capacity looked better than the HDL cholesterol pathway and related to a statistically significant reduction in risk in this cohort of coronary artery disease patients. It’s interesting in terms of how efflux may be a better marker than HDL cholesterol itself for how HDL relates to atherosclerosis.

Let’s look at a couple of studies. I’m going to start with a niacin study, the HPS-2-THRIVE study. This is the largest ever randomized trial of the effects of ER niacin on the safety and cardiovascular disease events to follow in diverse high-risk patient populations. The reason I like this trial so much is HPS was the study I think that showed that LDL lowering no matter what your baseline LDL was is beneficial in relating to events to follow. Whereas the HPS-2-THRIVE trial was done by the same group of investigators to look at the HDL question now looking at niacin.

Among those who tolerated this slow-release form of niacin for eight weeks, 76 remained compliant with the active treatment after three years versus 85% that were allocated to placebo. The retention rate was pretty good here. Remember, niacin is not a great friend for the patient. Many side effects are diverse related.

But this form of HDL increased the risk of myopathy among patients on statin therapy, particularly in the Chinese and that was some of the discontinuations that occurred in the HPS-2-THRIVE trial. There were no clear adverse effects on the liver, but all the other known niacin effects on the skin and the GI tract were confirmed, and also an increased risk of infection.

The effects of this four-year intervention on vascular events were published in 2014 and here are the data. Those patients randomized to niacin-laropiprant which is a slowly ingested form of niacin had no benefit on cardiovascular disease events to follow over the four-year period of observation. If you will, a failed trial to show the benefit of niacin which is one of the major drugs to raise HDL.
When we look at drugs to choose we choose niacin because it’s most effective in raising HDL. Fibrates are somewhat less effective. Statins have a little bit. Resins are a little bit effective. Oral estrogens are about as good as high-dose fibrates. PCSK-9 inhibitors are a modest 5 to 10% reduction. CETP inhibitors really were a major effector of HDL levels. And I’m going to come now to what I mentioned a few slides earlier on blocking CETP and how it affects atherosclerotic cardiovascular disease that comes to follow.

Torcetrapib despite a major effect on HDL cholesterols increased mortality and the study was terminated and the outcome abandoned in terms of the primary outcome. This increased mortality. Interestingly enough, it may have been from an increased risk of cardiovascular disease events.

Dalcetrapib, the phase III trial was stopped prematurely and I’m going to show you that data in a moment.

Anacetrapib, the phase III trial had a relative reduction of 9% which was statistically significant, but the benefit was not related to the HDL cholesterol change. It related to the modest ApoB reduction that occurred in patients with the CETP inhibitor.

And finally, evacetrapib was stopped early because of failure to predict a positive outcome to follow.

Let’s look at one of these trials in detail. I’m going to use Dal-OUTCOMES. Fifteen thousand six hundred patients with stable coronary heart disease after a recent acute coronary syndrome. Fully recruited. The background LDL lowering was with atorvastatin. Patients were randomized to dalcetrapib 600 versus placebo. The primary outcome was morbidity and mortality with patients with clinically stable cardiovascular disease after - - and long-term safety profiles.

Here’s the benefit of HDL. Boy, look at that. The levels are around 43 to 45 going up to levels of 55 approximately at the terminus of the study. A major - - also seen a placebo a little bit, but this effect here is merely a 30% increase. LDL cholesterol is not changed by dalcetrapib. That’s why I like this study because LDL cholesterol ApoB wasn’t changed, but HDL was changed. Let’s go forward. Look at the outcome. Wow, it’s hard to see any outcome trial that shows the superimposition of the two treatment groups in more of a dramatic fashion of this particular trial. And no benefit at all.

And this reminds of me explaining the absence of the benefit of raising HDL on atherosclerotic events. Yes, HDL may affect cholesterol efflux and reverse cholesterol transport. But the CETP trials I think inform us about one thing about HDL metabolism.

What’s the garbage that’s collected? Let’s say reverse cholesterol transport is effective in causing a benefit or resulting in a benefit. When you block CETP you block the transport of HDL cholesterol-containing cholesterol to the ApoB containing particles to get it back to the liver in a manner that probably represents the major pathway, not the HDL direct pathway through SRB-1. And it makes me think that increasing the HDL levels is like putting in the garbage truck.

You picked up the garbage, but now you’ve not delivered it as adequately to the liver and that increase in HDL cholesterol in the plasma relates to the defect in cholesterol delivery. And that’s a hypothesis and I’m sure there are lots of smart basic scientists and clinical investigators who are thinking about this now going forward in terms of additional HDL therapies.

And here are all the potential pathways by which HDL potentially could be modified favorably by a series of peptides, phospholipids, agonists, and ultimately, some genetic modifiers going forward. And I’m not
going to review this list, but nevertheless, there’s a lot of work still going on with HDL raising therapy, and perhaps one day we’re going to see the benefit of these therapies on HDL and cardiovascular disease to follow.

The evidence is now overwhelming that low levels of HDL cholesterol don’t cause coronary heart disease and drug treatment is no longer indicated. But why not then increase HDLs in other heart-healthy ways since most of the reasons for low HDL, to begin with, are in fact acquired? Well, heart-healthy ways. Exercise. Less than a 10% benefit from that and you need weight loss and the weight loss is less than 10%. It really relates to the amount of weight loss needing to be achieved. Sustained weight loss of 3 to 10% without exercise and here about a 10% effect is needed with more weight loss more beneficial.

Alcohol is a good way to raise HDL, but not a good prescription to be written in our clinics. I’ve had people that have a lot of atherosclerosis and they drink maybe a glass of wine once a week. I might say maybe a little bit more alcohol with your HDL can impact your risk a little bit, but I don’t have control trial data to recommend that. But I think you have to do that cautiously.

But anyway, the higher doses you use of alcohol means the more you drink the higher your HDL cholesterol level is, but that’s something we don’t want to accomplish in our patient population.

And smoking cessation is ultimately a 5 to 10% benefit on HDL cholesterol levels, not great, but it is there and something of course we want all our patients to do.

I’m going to stop there and thank you after a series of presentations with four objectives to relate how we define hypertriglyceridemia. And the problems in defining. Does atherosclerosis relate to triglyceride levels? Is that a causative effect or is it back to the association? Ultimately, the multiple issues related to management in patients with moderate hypertriglyceridemia and also, severe hypertriglyceridemic patients. He or she is a different patient. We have to approach them differently than just moderate hypertriglyceridemia.

And finally, the HDL story I think brought up to date in terms of where that field is at. Right now, heart-healthy strategies to modify HDL cholesterol are the best we can do.

I want to thank you for your attention and for subscribing to our certificate course and I hope it’s all going well for you as we go forward.

**Moderate Hypertriglyceridemia Patient Case**

DR. ECKEL: Hi, this is Bob Eckel returning to be with you again here for the presentation of a couple of patient cases that relate to hypertriglyceridemia. The first case is that of moderate hypertriglyceridemia and the second one will be on a patient with severe hypertriglyceridemia.

Let’s begin with the first case of moderate hypertriglyceridemia. Remember, the definitions for moderate hypertriglyceridemia we define as levels around 150 and 500. And most of the guidelines support that range as defining patients with hypertriglyceridemia as having moderate hypertriglyceridemia.
This is a 54-year-old with a strong family history of type 2 diabetes and cardiovascular disease who has new-onset type 2 diabetes. She has treated hypertension. She’s been defined as being dyslipidemic. She’s on a statin and is referred for evaluation of cardiometabolic risk for CVD. She has known hypothyroidism which is treated and also, she has obstructive sleep apnea and is on CPAP.

There’s no tobacco. She uses alcohol rarely. She’s on a South Beach low carbohydrate diet. Almost no physical activity and she works at a desk job.

Lisinopril 20 milligrams daily, levothyroxine 100 micrograms daily, atorvastatin 40 milligrams a day, and metformin 500 milligrams twice a day.

Again, reminding you of the case. A 54-year-old woman with a strong family history of type 2 and CVD. New-onset type 2 with hypertension and lipid disorder on a statin.

Weight is 179. Waist circumference 96. Based on her height, the calculated BMI is 29.5 kilograms per meter squared right between that upper range of overweight and obesity.

Systolic hypertension is modest at 142/82. No xanthomas. No carotid bruits. No cardiac murmurs. The liver is 8 sonometers by percussion. Dorsalis pedis pulse is 1 plus bilaterally. A little bit diminished.

Here are lipids. Total cholesterol we don’t pay much attention to. Triglycerides are 340 in that mid-range of moderate hypertriglyceridemia. Low HDL cholesterol at 38. LDL cholesterol 104. It’s borderline, but she’s on 40 milligrams of atorvastatin. AST, ALT is normal. Creatinine of 1 defining relatively normal renal function. The urinary albumin-creatinine ratio is 75 milligrams per gram.

And by the way, we’re calling this historically microalbuminuria, but now the nephrologist and to some extent us cardiometabolic physicians are defining proteinuria as the amount of urinary protein using urine albumin-creatinine ratio.

A1c of modest elevation at 7.4%. TSH normal at 1.6 milli-international units per liter.

First questions. Should triglycerides of 340 milligrams per deciliter be treated? Well, let’s look first of all at which approaches we might have to consider and we think of drugs, don’t we? Her South Beach diet would tend to be one that would lower triglycerides and although I don’t favor low carb diets for particularly long-term use. She would have maximum triglyceride-lowering on her current diet.

Fibrates. We’ve reviewed this during our lecture. Some up to 40% lowering depending on the initial value. Omega-3s up to 35%. Niacin which again is something we should not think about in this woman with new-onset type 2 diabetes. It’s up to 30%. And statins up to 35% with high ends getting a better effect. She’s on 40 milligrams of atorvastatin, so we shouldn’t be expecting much more triglyceride effect by modifying her statin dose. And the low end has minimal or no effects such as - - at 5 or 10. Those statins do not lower triglycerides.

Now, what if we think about the efficacy of triglyceride-lowering drug classes on CVD outcomes in randomized controlled trials? By the way, this was just recently published in Current Opinion in Cardiology in 2021. This analysis looked at the fibrate class, niacin, omega-3 fatty acids in low dose form and in high dose form. We’re not looking at statins here. We’re looking at triglyceride-lowering drug classes on outcomes.
With fibrates, they’re doing a meta-analysis through a randomized control trial showing an effect only on nonfatal MI, but the effect is a risk reduction of 20%. We can’t ignore that. And if we look at high dose omega-3 fatty acids a risk reduction of some 16%. There are only two trials that we turn to here. We really are looking at a benefit of ultimately 16% lowering.

Now, ultimately, the amount of triglyceride-lowering in many of these trials is fairly modest and the triglyceride-lowering effect doesn’t relate to the benefit. But look at the niacin trials and the omega-3 at low dose trials. No statistically significant relative risk reduction in those trials. We need to really carefully consider the choice of drugs.

And although the fibrate trials showed a benefit on nonfatal MI, there was no benefit related to the amount of triglyceride reduction. In other words, the more you lower triglycerides it didn’t relate to the benefit.

Now, the second question, and we’re going to return to all these questions in the end by the way in terms of what the correct answer might be. What about non-HDL cholesterol versus LDL as a better goal for treatment? Well, here’s a comparison published in 2018 that relates the Kaplan-Meier curves of LDL cholesterol and non-HDL cholesterol on specifically CVD or mortality. Here’s the LDL cholesterol curve over here. He’s the non-HDL cholesterol curve. And I can’t put one on top of the other, but you have to believe me that non-HDL cholesterol gets these various ranges. Particularly, the higher range tends to be better than LDL cholesterol in predicting the outcome.

And the reason for this is non-HDL cholesterol considers the impact of triglycerides or particles carrying the triglycerides on risk more than simply looking at the LDL cholesterol as a risk factor.

I think we can look at this and say yes, likely non-HDL cholesterol is going to be a better outcome to look at risk when we think of how triglycerides relate to cardiovascular disease risk.

The third question is when is ApoB useful and isn’t it the same as non-HDL cholesterol. Well, I’m going to share one trial that looks at the potential benefit of ApoB versus simply triglycerides and this is a classic study carried out in Quebec City, Canada. Ultimately, we’re looking here at the odds ratio for the development of coronary heart disease, looking at the lipoprotein phenotypes. These data were adjusted for age, smoking, alcohol, blood pressure, gender, and medications being utilized.

If we look at the classic Fredrickson-Levy classification of lipids, 2A is isolated LDL only. The risk for having a high LDL in this Quebec City study is ultimately about three times normal. Whereas if you had high LDL or high total cholesterol and high triglycerides the risk was reduced by having high triglycerides in the presence of a higher LDL or total cholesterol.

Anyway, reduced from 2.8, but still elevated to 1.7. But this is the type 4 phenotype which is isolated hypertriglyceridemia risk with no difference between normal lipoprotein patterns. And then if we turn to normal triglycerides versus high triglycerides this is what this looks like.

Ultimately, people with normal triglycerides who had the type 2B phenotype ultimately had the same risk. In other words, we corrected the fact that there are people here that had normal triglycerides in the setting of LDL cholesterol elevations and these people had the same risk as people with high LDL cholesterol elevation.
If we turn to this group, the 2Bs who now have high triglycerides and elevated ApoB ultimately now we’re looking at a three-fold increased risk.

The conclusion about these data is that the odds ratio of being hypertriglyceridemic relates to the presence of the 2B phenotype with elevations in ApoB that predict the risk of having high triglycerides. If you have normal triglycerides and a high ApoB you equal the risk of having high LDL cholesterol.

I think this is a fairly important study to look at historically. This is just an observational outcome study. But nevertheless, I think it takes us down the path of thinking that maybe ApoB containing particles is important.

Now, here’s to help answer this question and I presented this in our lecture on moderate hypertriglyceridemia. But when we look at non-HDL cholesterol and look at the relationship to ApoB. There’s a strong relationship looking at thousands of patients. But when we look at the ApoB level and how it relates to non-HDL cholesterol and we look at the 95th percent confidence intervals of that ApoB level at any given level of non-HDL cholesterol we’re looking at almost a two-fold increase in risk. At the same level of non-HDL cholesterol, but ApoB is two times higher.

Let me rephrase that. At the same level of non-HDL cholesterol, here we’re at a level of 190 milligrams per deciliter and ApoB can be elevated at 150 to 155 or could be very normal at a level of about 80 to 85 milligrams per deciliter.

How are we going to know which patient with hypertriglyceridemia if we’re using non-HDL cholesterol as a predictor of atherosclerotic risk is a person that has higher risk? And I’m going to contend that an ApoB of 140 would be a different kind of patient for me to approach than a patient whose ApoB is 85 or 90. Take that into consideration about the importance of ApoB, not in every patient.

If a patient has high total cholesterol and an LDL cholesterol by calculation you don’t need to measure ApoB, but in a patient who has high triglycerides where we’re using non-HDL cholesterol as an outcome variable to assess and treat to lower I think here the ApoB has tremendous value. These are not guidelines. This is echo opining. Take it for what it’s worth, but this is the way I’ve practiced medicine for over 20 years once ApoB assays became standardized and available for assessment.

Now, here’s the standardized vascular relative risk ratios of comparison of non-HDL cholesterol with ApoB and LDL from 12 independent epidemiological studies reporting relative risk ratios for both ApoB and non-HDL cholesterol. Here’s non-HDL cholesterol versus ApoB and I think this overall favors ApoB versus non-HDL cholesterol.

This is LDL cholesterol versus non-HDL cholesterol and this here favors non-HDL cholesterol versus LDL cholesterol. But look at ApoB versus LDL cholesterol. This is non-HDL versus LDL. Look at how strong ApoB is when it’s compared to LDL cholesterol. It’s suggesting that non-HDL cholesterol is better than LDL, but now ApoB becomes much better.

Now, Allan Sniderman, a colleague, and friend from Montreal has favored the replacement of lipid values for years and years and is now with apolipoproteins. He has a lot of merit I think with ApoB. But we’re not going to replace lipids in the near future with apolipoproteins.

I’m suggesting that in the hypertriglyceridemic patient that using non-HDL as a marker versus ApoB favors ApoB and when we compare LDL as ApoB we see a real win for ApoB over LDL. But I think it
overall shows a beneficial effect and favors ApoB versus non-HDL. And this wasn’t, by the way, in hypertriglyceridemic patients. This is in all comers. But I’m suggesting this relationship between ApoB and non-HDL cholesterol is going to be even stronger in our patients with hypertriglyceridemia.

The fourth question. What have the fibrate trials told us? Well, basically, I’ve reviewed this previously. They’ve told us that almost all of the fibrate trials have failed except one in which the benefit occurred from LDL lowering in people with moderately severe hypercholesterolemia.

And VA Hit is an interesting trial. We don’t completely understand it. Men only with low HDLs only with modest elevations in triglycerides who did benefit did not relate to triglyceride lowering. All of these other trials had no benefit nor was there an effect on triglyceride lowering that affected the outcome.

Now, here’s just looking at a subgroup of these fibrate trials in the pre-stain era looking at Helsinki Heart. Again, I told you it’s beneficial, but the benefit occurred through LDL lowering which occurs with fibrates when LDLs are very high like they were in Helsinki Heart.

The FIELD study had some statin drop-in, but there are very few patients. I don’t think hardly any were on statins, to begin with. This was in patients with type 2 diabetes, of course, and the FIELD trial failed to show a benefit in the trial as an overall trial outcome on the primary outcome. But in this sub-cohort here, ultimately, there was a benefit of fenofibrate in borderline terms that were statistically significant.

Keep in mind I didn’t mention this, but in the Helsinki Heart if you looked at the people with high TTs and higher rates of LDL with HDL, not TG to HDL the benefit was higher. But again, this effect was a benefit here from minus 34 to minus 74. It was mostly based on LDL cholesterol-lowering, not triglyceride-lowering.

Then the statin add-on was ACCORD where fenofibrate-simvastatin was compared to simvastatin and AIM-HIGH where niacin was compared to simvastatin plus or minus ezetimibe. The primary outcomes failed. And in the higher risk ratio a hint of benefit with a fenofibrate-simvastatin combination. And in the AIM-HIGH with niacin a hint of benefit where slightly different cut-points were used here.

Overall, it does suggest that the primary endpoint can be favorably impacted if we’re dealing with patients defined as dyslipidemic like the patient I’m just presenting with you now. Although, her HDL was 38, but still less than 42. But not less than 34 or 33.

These subgroup analyses of high triglycerides and low HDL do suggest a benefit of the fibrates and niacin, but we must consider the fact that these outcomes did not relate to the lowering of triglycerides in the trial.

High-dose omega-3 fatty trials aren’t any different. I showed you this slide in the presentation. Basically, the composition of the patients was fairly similar. The size of the trials differed to some extent with REDUCE-IT being smaller. I think JELIS was in hypercholesterolemic patients with primary and secondary prevention, high cardiovascular disease risk, elevated TGs and here elevated TGs and low HDL which would have predicted perhaps more ability in this sample size to produce an outcome.

The basic difference here was the EPA levels at baseline, similar between REDUCE-IT and STRENGTH. It’s higher in JELIS because it was done in Japan. The achieve levels are fairly similar for these two but much
lower in STRENGTH. And the drugs, of course, of choice, is DHA and EPA, EPA only here, and EPA only here.

When we look at the benefit I suggested to you before, the primary endpoint was a P-value of 0.001 in JELIS. The primary endpoint in REDUCE-IT was incredibly significant at this level and STRENGTH failed far from achieving statistically significant outcomes. And of course, there are reasons to explain this which we covered in the presentation on moderate hypertriglyceridemia that relates to non-triglyceride lowering effects of EPA only, not DHA that could affect the endothelium. That does not relate specifically to triglyceride-lowering effects.

Here are the questions. Let’s return to these in terms of the answers you may have given along the way. Should triglycerides at 340 be treated? Evidence indicates that triglyceride-lowering is beneficial. It’s not convincing from the fibrate trials looking at primary outcomes. But for patients who are at high risk and that could include patients with diabetes who have high triglyceride and low HDL cholesterols or have atherosclerotic cardiovascular disease icosapent ethyl should be considered.

I think the fibrate trials have failed to show that triglyceride-lowering is the mechanism for benefit. But EPA only I think does reflect other biologic mechanisms that currently relate to outcomes that we should consider EPA as a treatment strategy for these high-risk patients or people with existing CVD. That’s an FDA indication.

What about non-HDL versus LDL as a better treatment goal? I think in patients with high TGS and low HDL cholesterols, non-HDL should be a better treatment goal than LDL and that relates to the fact that these reflect in patients who were ApoB can be a marker for this better risk to assess non-HDL cholesterol as an outcome variable rather than LDL.

When is ApoB useful and is it the same as non-HDL? Well, I pointed out clearly it’s not the same as non-HDL, but it’s related to it. But it’s not the same as non-HDL cholesterol and may be more useful in individual patients than non-HDL cholesterol in assessing CVD risk. And again, these are mostly people whose LDLs calculate as normal or just modestly elevated whose triglycerides are elevated.

What have the fibrate trials told us? The CVD benefit is variable and mostly negative, and not related to triglyceride lowering. And that’s why I think this patient should be seriously considered for treatment with EPA and not a fibrate.

And are high-dose omega-3 trials any different? And I’ve suggested to you and I’m a bit redundant here, but EPA alone appears to be beneficial and it may relate to the EPA levels. And the DHA may not be harmful, but the EPA levels were not achieved, making that choice a less likely one for triglyceride-lowering which again did not relate to the outcome to follow. But it was beneficial.

Thank you very much for being with me on this case.

Severe Hypertriglyceridemia Patient Case

DR. ECKEL: Hi, Bob Eckel with you again. I’m here to present the second case. This one is a patient with severe hypertriglyceridemia defined loosely as levels of triglycerides above 1000 milligrams per deciliter. This patient is a 42-year-old woman with a history of hypertriglyceridemia recently found to have very elevated levels of fasting triglycerides. And she’s referred to you for further evaluation.
The patient has had a history of hypertension for five years plus her maximum body weight is 165. She eats one fish serving a week, whole grains two servings a day, fruit and vegetables four to five servings a day, drinks several glasses of wine a day, no tobacco use.

She walks around 15 minutes a day. She denies any abdominal pain which is important in patients with severe hypertriglyceridemia. She works as a desk clerk at a local bank. Her family history is relevant for type 2 diabetes in her mother and sudden death in her older brother who was age 53 at the time of his demise.

Her medications include fenofibrate at 145 milligrams per day. She’s also on omega-3 fatty acids 1 gram daily and she’s on Ortho-Novum 777 35 micrograms of Ethinyl estradiol orally as a birth control method.

Again, a 42-year-old woman with a history of hypertriglyceridemia was recently found to have very elevated levels of fasting triglycerides and referred to you for evaluation.

Weight 172. Waist circumference 32 inches. BMI 26.9 kilograms per meter squared. It’s probably normal, but probably a little bit overweight. She has eruptive xanthoma on her upper trunk. No lipemia retinalis. No carotid bruits or cardiac murmurs. Her liver is borderline at 10 sonometers and palpable below her lower ribcage. No abdominal tenderness. No lower extremity edema.

Total cholesterol looks elevated at 312, but we can explain why. It’s because her triglycerides are 2860. Now, keep in mind every lipoprotein has some cholesterol, some triglycerides, some phospholipids, and ultimately, proteins. They all have apoproteins.

But when the cholesterol is 312 and triglycerides are 3000 you don’t have to worry about the cholesterol. Because the chylomicron which is - - particle for the most part is pulling a little bit of cholesterol with it. And her VLDL cholesterol level is probably a little bit elevated also. Her HDL you’d expect to be low with triglycerides in this range and it is at 32. Hemoglobin A1c is 6.8%. We have little evidence of glucose intolerance at least here. Her hepatic transaminases are normal. Creatinine is normal at 0.9. TSH is normal at 1.6 and her urine albumin-creatinine ratio was negative. She has no proteinuria at all that’s related to per presentation here.

What do you think is the most likely explanation for this phenotype? Does she have familial chylomicronemia? Does she have excessive alcohol intake? She’s drinking a little bit and moderately actually. She’s on oral estrogen. She’s undiagnosed type 2 diabetes and she has a genetic form of hypertriglyceridemia plus acquired factors. Let’s ponder that and you make your choice.

What’s the best management strategy for this patient to reduce her dietary fat intake to 20% and substitute 2 grams twice a day of omega-3 fatty acids for the 1 gram she’s currently taking? Reduce her dietary fat intake to 20% of total calories and discontinue alcohol and her oral estrogen therapy.

The third option is to reduce her dietary fat intake to 20% and substitute 2 grams twice a day of omega-3 fatty acids for the 1 gram daily that she’s taking. Discontinue the alcohol. Discontinue the oral estrogen and add rosuvastatin 40 milligrams daily.

The fourth option is to reduce her dietary fat intake to less than 5% of calories, discontinue alcohol and oral estrogen, and measure her fasting triglycerides every three days.
The likely fifth option is to reduce her dietary fat to less than 5%, discontinue alcohol and oral estrogen, and instruct her in basal-bolus insulin administration.

What do you think the best choice is here? Let’s look at her plasma and this is what it looks like. This is creamy plasma represented by chylomicrons. If the lab spins that down, the chylomicrons will float and the plasma underneath it will look a little bit more like the right. Maybe a little bit turbid because some of the VLDL is going to be still there.

But I’m going to turn to a classic paper by my mentors in Seattle many years ago from John Brunzell and Ed Bierman where they showed if you looked at the presence or absence of chylomicrons in fasting plasma when levels get up to 1000 very few people have no chylomicrons present.

But this is a log scale. Keep in mind this goes up to maybe ultimately 2000 here. Occasionally, patients in this arrangement above 1000 don’t have chylomicrons. This is, by the way, separating chylomicrons by ultracentrifugation. This is not simply looking at the plasma - - levels. This is looking at chylomicrons per se.

But here some people are in the range of 500 to 100 having chylomicrons, but when you get up here in ranges above 1500 or 2000 almost everyone has chylomicrons.

The idea here is chylomicronemia is a condition in which the chylomicrons are present after an overnight fast. The most common cause of this is severe hypertriglyceridemia, the historic type 5 hyperlipoproteinemia which is a genetic etiology of hypertriglyceridemia plus acquired factors that relate to that.

Here’s the concept that we covered in the lecture earlier of saturation kinetics. The metaphor is a sink of water where the faucet is turned on to a modest extent. Where the drainage from below the sink through the drainage aspect of the sink. The input of water above equals the outflow and this is the relationship we have with normal triglyceride metabolism. Here is the production of VLDL particles shown here with ApoB, ApoC3, and ApoC2. These particles are produced at a rate that is ultimately consistent with removal. The rate of production relates to the rate of removal.

Now, the enzyme lipoprotein lipase is the rate of removal. If you think of basic biochemistry the substrate concentration of which is half of the VMAX, the total enzyme capability, is only 90 milligrams per deciliter. At that level, production equals removal and everything looks good.

But when removal starts to become a bit impaired, the production rate, particularly if it goes up, is going to reach a level in the sink that goes a bit higher. And finally, when you reach the VMAX of the enzyme shown here at the plateau, ultimately, now you’re dealing with saturation kinetics. Where the rate of production, the liver contributing VLDL here and now the gut contributing dietary fat in triglycerides through chylomicron production gives you a saturation kinetic example where triglyceride clearance is saturable, the sink is full, and the water flows on the floor.

And again, as I mentioned in my lecture, this metaphor has been a good way for me to present the patients’ problems to them to have them understand why their triglycerides have now gone up substantially over maybe a brief interval.

And one thing I often mention when teaching the medical students. If you send a patient from your clinic home on Friday with triglycerides of 500, ultimately like here, where it’s 500 or around this range.
Remember, this is a log scale here. You send them home on Friday and on Monday they come in after watching 15 NFL football games over the weekend, drinking a couple of cases of beer, and eating a high-fat diet from your fast-food place. You can have triglycerides at 2000 or 3000 on Friday because you were already operating here on Friday. And now, dietary fat is accumulating because of all the environmental influences occurring over the weekend.

This is important for you to understand clinically. That’s why when triglycerides above 500 is recommended by all the guidelines that you take steps to lower triglycerides even though the patient may not be chylomicronemic at this point. Let’s continue forward.

We showed this slide earlier. Familial chylomicronemia is basically one in a million. The additional genes are shown on the next slide. Anyway, ultimately, these are the risks that occur.

I’m going to go back up and reintroduce this slide.

In thinking about the causes of severe hypertriglyceridemia. Familial chylomicronemia is rare. It’s one in a million cases and has these various characteristics that we also need to take into consideration in patients with acquired forms with a genetic predisposition. That’s pancreatitis risk, lipemia retinalis shown here, and eruptive xanthoma shown on the gluteal region shown here.

Now, ultimately, the acquired disorders that relate to genetic risk we’ve talked about previously and we’ll come back to those in a moment.

But in terms of answering the treatment question, here’s the paradigm for the approach therapeutically for people with severe hypertriglyceridemia. No fat or less than 5%. You need a dietician working closely with you on this. It’s not a long-term dietary manipulation, but it’s for the short term. No alcohol, no oral estrogens, by the way. Discontinuing all triglyceride-lowering drugs is debatable and I covered that in my presentation of why and why not. Less than 5% dietary fat relates to a 25% reduction in triglycerides daily when you have saturation kinetics.

Let’s take a level of 5000. If we restrict dietary fat to 5% and if we expect a 25% reduction daily we’re talking about, ultimately, a reduction into the high 3000 range in one day and you’re going to be approaching maybe close to around 1500 by three days. That’s why I measure triglycerides every three days to look at dietary compliance and see if this rate of reduction is ensuing.

Then I tend to restart lipid-lowering therapy here for two reasons. One I think is the drugs aren’t working here. The fibrate lowering drugs are not working here, including the high-dose statins. I don’t stop the statins because of the LDL effect that the patient was on already.

But then, also, when you restart them you see a fairly dramatic fall with a fibrate or omega-3 fatty acids or combined therapy over the next three days. And ultimately, these drugs work on the liver and that’s a rapid effect. The half of VLDL is in a matter of hours, not in a matter of days - - once you have saturation kinetics.

IV insulin, heparin, or plasmapheresis add very little value. If the patient has to be hospitalized, particularly because of diabetes and you need glycemic control IV insulin through a drip makes a lot of sense. All heparin does is cause the triglycerides to be clear in the plasma, but it releases a storm of free fatty acids that could be ultimately multisystemically damaging. Heparin makes the doctor feel better, but ultimately, it’s not really the pathway that you want to go down to really lower triglycerides.
Plasmapheresis works for one exchange, but you got to do it again in a few days. Because it only reduces the level by maybe up to 1000 or 1500 and you’re not going to recover that level unless the 5% fat restriction is continued. And typically, I rarely turn to this clinically.

Once the triglycerides are under 1000, - - dietary fat and avoid simple sugars, particularly those with diabetes. And alcohol based on the rate and the amount of TG decline. I wouldn’t allow the person to drink until TGs are well under 500 or 400 milligrams per deciliter.

That’s our case discussion for this particular case. The answers to the questions. Let me return to the questions. This patient likely has a genetic etiology of hypertriglyceridemia plus secondary causes. Type 5, historically, is probably 95% of severe hypertriglyceridemia that you’re going to see. The familial form needs to be recognized and patients presenting at a much earlier age and often in childhood or adolescence.

And the second answer relates to the management strategies that relate to less than 5% fat, not IV insulin, and ultimately returning to the measurement of TGs every three days. And of course, in this particular woman, stopping the oral estrogens and stopping the alcohol would be the next best thing beyond the low dietary fat intake.

Again, thank you for your attention. It’s been great working with you in this space of hypertriglyceridemia both moderate and severe in terms of the importance of patients at risk for cardiovascular disease or at risk for pancreatitis which at times, of course, can be a fatal disorder. Thank you very much.