VIDEO_ Diet Doctor Podcast with Dr. Ron Krauss (Episode 9)

Dr. Bret Scher: Welcome to the DietDoctor podcast with Dr. Bret Scher. Today I'm joined by Dr. Ronald Krauss. Now Dr. Krauss is really a luminary in the field of lipid research and he's got a laundry list of accolades with over 450 publications mostly in the field of lipidology.

And he's the director of atherosclerosis research at the Children's Hospital Oakland research Institute, he's a professor of medicine at UCSF, professor of nutritional science at Berkeley, he's been involved in development of cholesterol guidelines, what was called the ATP program, in the past, he was the founder of the American Heart Association Council on nutrition, physical activity and metabolism.

He definitely has one foot firmly planted in the cholesterol world and one foot firmly planted in the lifestyle and nutrition world. And I think that's one of the things that makes his perspective so unique. Let's be honest we can all kind of get too entrenched in certain paradigms, one paradigm that all LDL is bad no matter what, one paradigm that LDL does not matter at all.

And clearly I think neither one is truly accurate into much more nuanced discussion and that's what I really appreciate Dr. Krauss' approach to this and his knowledge. And let's face it, I mean he was the pioneer in identifying the size and the density in the different varieties of LDL cholesterol. So when it comes to understanding the nuance and that not all LDL is the same, he is definitely the man to talk to.

So we cover a lot of ground in this discussion about LDL, about lipids in general and of course what it means to your lifestyle and how your lifestyle impacts that. So sit back, get out a pen and paper, there's a lot to digest here, but I really hope you enjoy this interview with Dr. Ronald Krauss. Dr. Ronald Krauss, thank you so much for joining me on the DietDoctor podcast today.

Dr. Ronald Krauss: It's a pleasure to be here.

Bret: Now in the intro you've obviously been around the world of lipids in lipid research and very proficient for a number of decades. You've seen a number of changes in the world of lipidology and the world of nutrition and lifestyle.

And one of the things that I appreciate most about you is that you were the founder of the AHA Council on nutrition, physical activity and metabolism and you've been very involved in how nutrition affects lipidology. Give us if you can just a brief

overview of how you've seen the sea of nutrition and lipids in the interaction sort of change over the time that you've been involved in this.

Ronald: Let me do that in the context of my role with the American Heart Association. Early on I became involved with what was called the Nutrition Committee that among other things set guidelines for heart disease prevention with diet periodically. And one of my first exercises was to update those guidelines when I became chair of the Nutrition Committee.

And I'd inherited a kind of a set of rules that were implemented over the years that emphasized reducing fat and replacing the fat with carbohydrate. It was this low-fat method. This was not that long ago. Well, for me anyway, it was 20+ years ago. That was the prevailing recommendation. But at the same time I was doing research trying to understand the role of lipoprotein metabolism in atherosclerosis as it's affected by diet.

And so one of the first studies that I did to address that was to test the effect of the standard low-fat high carbohydrate diet in a group of volunteers who had a lipid profile that most of whom were normal to start with. And it was really to see whether or not we could improve certain features of a profile. We can talk about that perhaps in a few moments.

But what I found was to my surprise that the standard low-fat high carbohydrate diet actually worsened the lipid profile in a substantial subset of this population very strongly related to heart disease risk outcomes, higher levels of LD particles and higher levels of triglycerides which is another risk factor for heart disease. And it wasn't a complete surprise because looking back over the years others have shown that high carb diets can induce a high triglyceride level and the effect on the LDL was really what was quite surprising.

And as a result of that and further research that I engaged in to explore that mechanism further, I changed my views on what the proper diet should be for heart disease prevention. One issue was individualizing the approaches to people based on their metabolic profile. So there's an issue of not everybody needs the same diet. But for the overall recommendations I tried to move the Heart Association a little bit further away from the low-fat approach and I wrote another set of dietary guidelines five years later that reflected that.

But that was like trying to move a mountain, because the amount of investment in that old message was so strong that there was resistance to doing that. Overtime I think with further research if we can talk about, that approach I think has been challenged by many others.

And that change I think is now in play, although organizations like the Heart Association and even the US dietary guidelines that are charged with making public recommendations still up put a great deal of emphasis on the facts out of the equation, beginning to be more concerned about the carbohydrate trade-off. But I think it could be taken even further.

Bret: Yeah, there's a lot there and just in that one statement that you made that these guidelines were already set in place and believed to be true and yet you had research showing not only was it maybe a neutral effect of what the guidelines were, but a potentially deleterious effect.

Ronald: For a significant subset of population, not for everyone, but enough people to be concerning.

Bret: Right, and yet still they haven't come 180, which you think they would once the research came out, because once you're entrenched in the guideline like that, it's hard to back out of that room and change your tune.

Ronald: And then you have to look at the overall evidence, not just about what happens to lipids on various diets, but how do those diets relate to heart disease outcomes. And I've been more engaged recently evaluating the literature that addresses that. Some of this sure you've already talked about in other contexts, but it's clear that the evidence that was thought to exist linking saturated fat in particular to heart disease risk didn't hold up very well when we looked at the actual literature.

There are issues about what one substitutes for saturated fat potentially being an important factor. And there's now more of us, generally women, that the substitution of carbohydrate for saturated fat, which was really what was a consequence of the earlier guidelines... People were encouraged to drop saturated fat and many times they were eating the wrong kinds of carbs in considerable amounts. That approach I think has been shown to be a factor in increasing heart disease risk--

Bret: Increasing heart disease.

Ronald: So this amount of research has really converged I think with a broader look at heart disease risk and its relationship to diet, giving us a little more latitude on the fat side. I think it still could go higher. And more attention to the carbohydrate side with particular emphasis on simple sugars. The total carbohydrate load is still a matter for discussion as to how deliver recommendations for overall carbohydrate intake to the population.

There are so many nuances, I mean there's the issue of reducing carb itself overall, there's the issue of using carbs that are really whole grain and whole grain itself is

something that many people don't even quite understand. The whole grain that works is where the kernels of the grains like brown rice or whole kernel rye, where you haven't grounded up, that's fiber rich source that is probably okay for a number of health outcomes.

But that's not what most people understand and they wind up just going overboard on carbs and the one way of dealing with that is just to tell them to drop the total carbs. I tried to get into what kinds of carbs.

Bret: Right, the quality of carbs matters.

Ronald: It does matter. It's very hard to convey that information in a way that the public can implement. The food industry has not been particularly helpful--

Bret: I wonder why.

Ronald: Well, they were initially on board with the low-fat message. That's in fact what took us down... Took my predecessors down the path of making incorrect public health recommendations and the food industry was helping that along by providing high sugar low-fat products like SnackWell's and that was the classic example of going the wrong way on the carb story to kind of educate people and the food industry trying to provide the healthful form of something that food industry could market is very difficult since most of what we are now trying to promote in the current approach which meshes with some of the aspects of the dietary guidelines is to think about foods and as much as possible to think about foods that you don't necessarily have to get in the box.

Because once the food industry gets involved with packaging and processing things change and there isn't a strong advocacy on the marketing side for the kinds of foods that carry a lot of health, the whole grain products, products that have the kinds of things that you get from the vegetables and fruits, everybody talks about that. But when you go to get your food in the supermarket and you get it in a box, it doesn't necessarily have the same qualities.

Bret: But yet those boxes can sometimes say heart healthy or gluten-free and low-fat.

Ronald: It's very confusing.

Bret: So talking about carbohydrates, proteins and fats we should be talking about foods, like you're saying, they should come from the ground like a vegetable, should come from an animal, should not come from a box. And simple messages like that sort of get lost.

Ronald: Yeah, and I think there's more and more recognition of that approach. But it's very hard to deliver that to the public in an actionable way, given our current distribution of food, you know, where the supermarkets are and who can buy the groceries and who can afford to buy for example fish, which is another thing that you think adds value in the diet. These are all kinds of approaches that are not always easy to implement for social and economic reasons.

Bret: And it doesn't help that age-old subsidies that have been helping promote sort of the wrong types of foods and not the right types of foods and that's a whole another battle.

Ronald: That's right, absolutely.

Bret: I want to focus a little bit more on the LDL. So you mentioned a study that you did to help sort of change the tune of the AHA and the big concepts are - are we following the right markers? Because anybody goes to their regular doctor even their cardiologist and the first thing they want to talk about is the LDL-C. Is that the right marker to follow?

Ronald: Well, it's not the best marker. LDL-C stands for LDL cholesterol and that is the portion of the cholesterol in the blood that is carried around in the blood on particles which are LDL particles.

So LDL-C is potentially a marker for the numbers of those particles, but it doesn't fully reflect the numbers of those particles and it's in numbers of the LDL particles more than the cholesterol content that determines atherosclerosis risk. So traditionally over the years LDL-C has served as being an easily measured laboratory test. I was involved when I was at NIH for a number of years at the time that the LDL-C test was actually developed.

Most labs actually calculate it, it's not a super accurate measurement, that's another issue, but it took hold because people were able to use it in large population studies and in clinical trials and in the literature therefore is heavily weighted towards LDL-C as sort of be-all and the end-all.

Yet it's the particles that matter and there are a huge number of situations in the clinic, particularly in individuals who have metabolic syndrome, which is a constellation of risk factors that include high triglyceride and low HDL where LDL cholesterol does not really reflect the true atherogenic potential, the true cardiovascular risk, because in that syndrome there can be an increased number of LDL particles, but they are small particles which have less cholesterol and that's really been the focus of my research.

It was identifying those particles and showing that they are predictor of risk even when LDL cholesterol was normal. And so that's a significant percentage of population where LDL cholesterol does not truly reflect the risk.

And it can sometimes over-represent the risk because there are a set of particles on the other side of the spectrum that are large LDL that actually have more cholesterol, but their association with heart disease risk is really quite low. In fact there are a number of studies which... People still don't really register that there is really no obvious relationship of those particles to risk.

Bret: So some would argue if you cancel that out by accounting for the number of particles then the size has less of an impact. But I think you would disagree with that.

Ronald: Well, it's how you frame the question. The numbers of LDL particles is a desirable metric for heart disease risk and when the particle number is elevated in general, that tends to be correlated with increased levels of small LDL particles. The number of individuals in the population who have high LDL particles based on the larger LDL is a minority.

So when one measures LDL particles and says the size isn't important, well it is because those are small LDL particles you are measuring, but what matters is not so much the size, but the numbers of those particles. So people confuse those concepts and to me it's a relatively simple notion to say that the total number of LDL particles is what one should be concerned about and that when the particle count is elevated more often that represents his small LDL.

Bret: When it's elevated and they're predominantly the larger LDL is that usually in the metabolically healthy person who has elevated LDL for some reason but not because they have insulin resistance or diabetes or metabolic syndrome?

Ronald: Well, there is a category in the population that fits the criteria that you've just described and who not only have a health metabolic profile in general, insulin sensitivity, normal triglyceride levels, HDL levels are high, that's another marker of lower heart disease risk... that constellation can be associated with increased levels of larger LDL particles. But here's where it gets a little thorny because there are people out there who have genetic disorders that cause their LDL levels to skyrocket.

And that's because the LDL is not being taken out of the blood stream effectively. And those people can have large LDL particles, but they are hanging around too long. And in fact the theme that I've been trying to promote is an underlying concept to help people grapple with these distinctions is atherosclerosis which is the basic phenomenon that leads to vascular disease and heart events and strokes is built on the accumulation of LDL particles in the artery wall.

And if the particles in the blood are circulating long enough, there's going to be a greater tendency of those particles to wind up in the wrong place. So it's what we call the residence time. And the smaller particles have a long residence time by virtue of their structure.

And we don't have to go into the reasons for that, but it's been well-established that they are cleared much less effectively than larger particles, they hang around longer and that's clearly I think in my view and those of others a basis for understanding why are they associated with risk. Well, if you have a defect in the receiving end of liver--

Bret: So the LDL receptors.

Ronald: The receptors are defective that can also lead to increased circulation time and there are the LDL particle number still is important, but they could well be larger particles. Because the defect is not in the particles, it's in the receptor. So that's why I do what I do. Cardiologists such as yourself interested in this field have a great role in helping to elevate recognition of prevention through LDL and other lipid modification.

Use of statins for example was greatly enhanced by the involvement of the cardiologists in clinical trials. The lipidologists can go into a little more detail than is usually possible in other clinical settings. Basically in part using the right kind of tests that can distinguish these different particles and making clinical recommendations on an individual basis.

I see patients and I can make generalizations and we've made some here about large and small LDL. But I see patients who have large LDL and I worry about them sometimes because of other factors... genetic--

Bret: So if they have familial hypercholesterolemia...

Ronald: Yeah, a family history of heart disease or if they have other known risk factors I tend to take them more seriously and hedge one's bets and I say, "Don't worry about this". And in fact in the low-carb community, your listeners, a significant subset of people would like to think that LDL is not harmful at all, because after all the benefits of low-carb diet are so strong even when LDL goes up which sometimes can go up rather high in some of these patients, that that must be okay because the people are healthy and their metabolic profile is good and their insulin sensitivity is good, they don't have any coronary calcium.

So there's this tension about extrapolating the kind of work that I've done to an extreme saying that if you have this high LDL, particularly if they're large LDL

particles, you don't have to worry about it and I'm a little nervous about making that recommendation to every patient I see.

Bret: Sure, and that's understandable and as a cardiologist I get nervous into that setting as well. And a lot of it is just what we've been told for decades and decades. But I think to be fair this population is really underrepresented by the current literature that's out there. And we really don't know that the LDL studies have looked at standard American diets, have looked at low-fat diets, have looked at general population, haven't looked at this specific subset.

And I think that would be so interesting, that's the information we need to say is it safe or is it not. Now until then we still have to decide what to do that patient sitting across from us and that's when we have to incorporate the whole profile; their metabolic health, the size and density of the LDL, their HDL, the triglycerides and the other benefits they get from the diet and then make an individualized decision.

But can't say, "No, LDL doesn't matter forget about it". And in the same token can't say, "Any elevated LDL needs a statin right now". It's more nuanced than that.

Ronald: You framed that perfectly. I completely agree with that. That's exactly the right approach.

Bret: Are there other ways and things we can do to try and get an idea of residence time in someone who doesn't have-- or even in someone who does have FH? Because when you look at the FH subset, you know, it's not 100%, not everybody gets coronary disease in their 40s and 50s and there's some data suggest if you don't, you might live even a little longer. So how do we get a better sense of residence time?

Ronald: The short answer is we don't have a good test for that specifically. In fact I've been talking to colleagues who do studies of metabolic signatures using metabolomics on the aspect. We're interested in identifying molecules and the particles that might reflect their residence time and in principle I think there's a reasonable shot at being able to do that, but we're way far away from even initiating those kinds of studies. And so we are left with at least for the small LDL individual. There I think the data are sufficiently compelling to me that having an increased level of small particles does implicate residence time as a factor.

Bret: Now does small LDL tend to be a proxy for insulin resistance and pre-diabetes, or can you see them also separated from that?

Ronald: That's another very good question. I hang out a lot with people who are interested in insulin resistance, I'm actually an endocrinologist by training, and I was very close with the late Gerry Reaven who was the endocrinologist at Stanford, who

put that on the map, so insulin resistance does play a central role in many of the manifestations of the lipid disorders that we see; nitroglycerin high triglycerides, low LDL, and it does contribute to the small LDL trait.

Having said that, the overlap is not by any means complete because I tend to see a lot of patients in whom I can characterize all these metabolic features. I can speak at least based on that experience to the fact that there are people whose insulin sensitivity is really very good but they have a genetic predisposition to a small LDL trait itself, that there's something affecting lipoprotein metabolism that doesn't come through insulin resistance.

In fact there is a larger proportion of population I think who have the dyslipidemia. Those without insulin resistance in total, than those who are at risk because they have some insulin resistance alone. This is metabolic fate, with small LDL is really prevalent. We just did a study in healthy but somewhat overweight and obese men and the prevalence of the phenotype that is just they have mainly small vs large LDL was almost 50%.

So as one deals with populations that are more representative unfortunately of the average American in terms of body fat, waist circumference, these kinds of things that predispose to insulin resistance. We're exposing more of the small LDL phenotype, but then in many of those individuals when one tries to reverse it, and this is something we'll be talking about more in the talk I'm giving at this meeting, we can reverse that phenotype by reducing carbohydrate or reducing weight or both.

But there remains a residual group of people who appear to be genetically hardwired. Fortunately it's a minority. So the answer is for the most part there's an overlap, but there still are people who have an independent lipid trait that needs attention.

Bret: And is there any difference in outcome between the two as you're aware of?

Ronald: No, we don't know, because we don't have good integration of detailed metabolic measurements with the kinds of clinical data that are coming from outcome studies. The outcome studies rely on the high throughput inexpensive kinds of tests and it's even been hard to generate enthusiasm for another test, which I think has a role in clinical practices and it's Apo protein B, which is a marker in a number of number particles.

That's a pretty simple test to do and I've been an advocate for at least taking that step if not going further into measuring different particles themselves, but a lot of studies don't even have that measurement. And if they do sometimes they don't publish the results.

Bret: So it seems that consensus is starting to change certainly in the field of lipidology and hopefully in the field of cardiology, that LDL-P, ApoB are better markers than LDL-C and that knowing the size and density of your LDL particles is certainly helpful to inform lifestyle changes. But yet it seems like most people have to fight with their doctors to get those measured... Why the disconnect?

Ronald: Part of the problem and I've been indirectly responsible for this problem is the methodology and the nomenclature that has been used in the clinical laboratory, because I actually introduced the first clinical testing for this, which was electrophoresis procedure which was really not completely quantitative. It was a way of getting a semi quantitative assessment, but we're talking about different kinds of LDL in that measurement.

But then there were a couple of new methods including another one that I developed much further in terms of being able to quantitate the numbers of particles. But they use different principles, these methods. One of them is NMR, spectroscopy, my method uses something called Ion Mobility and we haven't yet joined forces.

So clinicians from the clinical laboratories can be confused as to what is they should be measuring, we don't quite know what the targets should be because there haven't been really extensive studies to establish anything like targets, although now the guidelines for cholesterol are an abandoned cargo anyway, so maybe they're not needed, which I tend to disagree with.

Subsidiary books are confused in part by the methodology and it's also a little bit daunting to see the information that comes through with these tests, because the way the reports are annotated while they attempt to be helpful, the clinicians I think still leave a lot of questions as to what this means. So what I've been doing is an N of 1 and others have been doing it more broadly but whenever possible as you keep people in these tests.

And once they get a feel for it, I think it becomes much more attractive to them. In fact when I first discovered that the worthy subclasses-- it's been now 30 years ago actually, I face a tremendous amount of assistance among my colleagues. It took about 10 or 15 years, believe it or not, of hammering away that this even exists, because people were not able to see it in their own laboratories.

I had this very, what they call "esoteric" at the time. Some people still call it esoteric methodology and they weren't doing it themselves. What happened was as the methods became more accessible and other people started to adopt them, they said, "Wow, this is obvious."

Bret: Right.

Ronald: And now it's in the textbooks and I didn't even get a credit for this.

Bret: You fought the battle for a decade.

Ronald: I fought very hard for this and I feel that I have at least gotten the small LDL trait as part of metabolic syndrome and insulin resistance some and established that now is in the Bible.

Bret: I guess one of the other arguments is someone say it's an added cost without a clear added benefit beyond non-HDL cholesterol. Because you're talking about the whole population and there's probably a subset where that may be true, but it seems like there's a huge subset where that still is not true, that people just don't recognize.

Ronald: Well, again it's hard to talk about the population as a whole based on my experience or anything even in the literature, because in my case I see people whom these other measurements don't adequately define risk and on the science side I sometimes have to deal with people who make all their clinical recommendations based on the list patient they saw or anecdotal evidence and I think there are problems there.

However my anecdotal evidence which I would give more credit to is that there are people come in and I just saw one last week whose father had an early heart attack, his lipid profile was small LDL and the lipids were perfectly normal. And in fact it's been very difficult to reverse that trait without medication.

So that's an example which I think is not uncommon of a genetic underpinning that's messed by standard lipid levels. And there are people out there like that picked up at a standard lipid test and who should be intervened on. Family history can be helpful but not everybody has an informative family history. It's not the greatest clinical test.

But there's another test by the way which I think deserves mentioned, that is part of this overall assessment, called Lipoprotein (a) or LP(a) which is another form of LDL type particle in the blood that has a very strong genetic determining factor. And what we found is a combination of people who have a role to the high level of this LPA.

And we think may be as much as a third of the population that has levels that potentially would increase risk of heart disease. If that's coupled with small LDL and there is any kind family history at all, people are dropping dead of heart attacks in their 50s. But these are not picked up by the standard lipids--

Bret: Not picked up by a standard LDL-C or LDL-P, but this informs you a little bit more about the type of LDL that's there.

Ronald: Well, LDL-P can help, but it's still not as specific as the small LDL measurement.

Bret: Right, so LP(a) tends to be a little more pro-thrombotic potentially, pro-inflammatory and-- does it also have a higher residence time as well?

Ronald: Yes, it is very slow clearance by the LDL receptor and it tends to get oxidized easily which is one of things that happens to small LDL as well that makes them more toxic to the arteries.

Bret: So a very important test to measure. Now the traditional teaching is you measure it once and there's really not much to do about it in terms of treatment. Now of course there's research been done with these antisense RNAs, but for the time being do we have much to address it?

Ronald: Not much. One of the treatments that is currently out of fashion, nicotinic acid, can lower LP(a), but the argument against it is we don't have evidence of lowering LP(a) with that is beneficial. Some of the new approaches, this anti-PCSK9 antibody that is used in high risk patients can lower the LP(a). It's one of the more attractive features although you can't get insurance people to cover it for LP(a) lowering, it's not a bona fide indication.

But you're right, without exception for the most part LP(a) is relatively fixed genetically. The value of it and I believe there is value at this meeting is to give a broader picture of the overall risk particularly in the context of situations where you're not sure whether one should be aggressively lowering LDL for example.

So this brings in the concept which-- I will take a few seconds to emphasize this absolute risk versus relative risk. So LPA increases the risk of heart attacks when it's elevated by as much as a factor of threefold, but it's pretty powerful. That's relative risk. But you're multiplying that relative risk by the absolute risk overall.

And so if the absolute risk based on every other measurement is very low multiplying that by three is still going to give you a low number. If it were zero, it would be zero. So what we do I think justifiably is to be more aggressive in lipid management and risk management in general to lower the absolute risk in patients who have high LPA and a strong family history.

In my experience again I've been doing this a long time and I have patients whose siblings dropped dead or had a stroke in her 40s who had high LP(a) and I've been treating them and they are now in their 70s. I think we have found a way to overcome that genetic risk.

Bret: That's a great point to bring up the relative versus absolute risk reduction because that's something that confuses people and confuses clinicians as well. Partly driven by Big Pharma I would say.

Ronald: Absolute.

Bret: They love to promote relative risk, it's a sexier number, a more catchy number.

Ronald: A 50% reduction in risk... isn't that great? If the risk is here, that 50% is small.

Bret: So it doesn't just apply to drugs, it applies to lipid markers as well. Now interestingly, I have to throw this out there... Up until a couple of weeks ago I thought LP(a) was something you could not change with lifestyle, because it was genetically set. I don't know if you're familiar with Dave Feldman at cholesterolcode.com and his colleague Siobhan Huggins.

She did an N of one experiment, which take it for what it is, an N of one experiment, where just changing her dietary consumption she was able to see a huge swing in her LP(a) which was shocking to me and I hope there's more coming on this topic because it's traditionally been taught you can't affect it with lifestyle, but here we have some evidence that maybe you can.

Ronald: So there are two features of that... I wasn't familiar with that particular story but there are two components there that I think are relevant. One is-- in fact I published on this... a way back to the traditional low fat high carbohydrate diet which was supposed to be good. It can raise LP(a).

So LP(a) can go up with high carb so the converse can be true as well, there can be some reduction. It tends to be relatively fixed i.e. the changes in general are small, but they are in the direction that if you go on this kind of diet with dropping carbs, that you may have some benefit.

But the second component is genetics because there's at least 50 different genetic subtypes of LP(a) and there are some that are more responsive to X and others that are unresponsive. There are some that we follow over time and they go like this and they go up-and-down and there are others that are rock-solid.

So there's a genetic component. It's one of the keys, one of the prime examples of a complex genetic trait that is very difficult to dissect on an individual basis. We don't have ways of knowing who has which genetic markers and how is that going to respond to that, but this may be part of the story for that N of 1.

Bret: Good point. So one other marker I wanted to bring up... Or I guess more than just a marker, is ratios. Because we talk a lot about individual markers and there's also an importance of ratio.

So I talked to Prof. Andrew Mente with the PURE study and one of the most interesting things about the PURE study was-- again it showed LDL-C is not a very good marker for cardiovascular outcomes and a better marker was to ApoB to ApoA ratio. And that was really the best one, but again not one that gets measured very often. So how do you see the role of ApoB to ApoA ratio?

Ronald: I think it has a lot of merit, because the numerator is a measure of number of LDL particles. In fact overall, not just LDL, but all of the atherogenic ApoB containing particles. That's good. The denominator is reflecting a protein that is responsible mechanistically for the benefit that has been attributed to HDL and heart disease risk. We can get into ApoA versus HDL cholesterol...

It's another example where the HDL cholesterol it's taking us down the path where that marker is not so informative because it's not necessarily reflecting something that can be reflected by ApoA1 specifically. So the ratio of ApoB to ApoA1 I think has merit as a risk assessment tool. In fact the ratio of HDL cholesterol also works pretty well as a risk marker. The problem is that we can't necessarily translate that risk marker to a target of treatment.

If you start treating a ratio you get into some potentially very inappropriate outcomes trying to resample raise the HDL has been shown... HDL cholesterol has been shown to be relatively... in fact completely ineffective.

Bret: Completely ineffective.

Ronald: Despite the fact that low HDL is a risk factor. Well we don't have the same confidence in ApoA1 as a measurement in ratio. It's reducing that ratio by raising ApoA, is that going to be beneficial? One would like think so, but we don't have the evidence for that. So I would put those ratios in the category of good markers for risk, but not necessarily using them, the ratios themselves as targets.

Bret: And that's another great point to bring up to differentiate targets on treatment versus targets with lifestyle changes. Because there does seem to be a significant difference. You can target the HDL with CETP inhibitors which have either increased risk or being totally neutral. So clearly the drug manipulation of HDL is not beneficial, but the nutritional manipulation and the lifestyle manipulation theoretically should have a different impact.

Ronald: Well you are doing the right things to risk by a proper lifestyle intervention, and that could be reflected by these ratios, by measurements approving, absolutely, whether they are markers or whether they are actually involved in delivering the benefits of those interventions, we don't know, but they go along with the territory.

For example we showed years ago one of the earliest studies that was able to show changes in HDL was looking at the effects of physical exercise. Peter Wood at Stanford was the pioneer of that work and we were collaborating with him. In fact when he learned that exercise could raise HDL levels he convinced me to go out and start running. I was actually very sedentary up until that time. And I decided, "This is going to raise my HDL."

And of course in retrospect it's probably the running and that raise of the HDL that was beneficial. But no, you're right, that axis of working on a metabolically healthy nutritional lifestyle intervention, when it causes changes in these markers, I think it's more or less a reflection of the benefits of those changes.

Bret: Yeah, because one of the changes is increase in fat in the diet and specifically saturated fat can dramatically improve the ApoB to ApoA1 ratio.

Ronald: Yeah, you have to be careful. Yes, one can do that or can keep the ratio high if it's high to begin with and that has also been shown in people that you can raise the ApoB and the ApoA1 together. Our studies, when I look in the literature, would suggest that's probably benign, but we don't know for sure if that's true for everyone.

Bret: So we touched on HDL here a little bit so I want to talk a little bit more about HDL. So when people have an elevated HDL level whether it's, you know, 70 to 120 and it's naturally elevated, not on any drugs, would you count that as a beneficial effect or would you say we need to know more about it? Do you want to know if it's the specific HDL too, or do you want to know what their ApoA1 is or some greater assessment of HDL function rather than the absolute number?

Ronald: Well, there can be a measurement, there is actually a management of HDL function that does appear to reflect its benefit on cardiovascular risk, atherosclerosis development and that is the ability of HDL to promote the efflux removal of cholesterol from tissues and particularly the cells and macrophages that would lead to plaque development and progression and there are tests that are being developed and a lot of that have to be measured, those you're not clinically out there, they are more for research purposes.

And what we've been trying to do, what many people have tried to do, including myself, is to try to identify a particular measurement that we can do in the blood of a more standardized nature that doesn't involve having to go into the lab and use cells

and culture. And it hasn't been a clear match, so making a shorter answer, we really don't have a particle that we can identify.

Having said that I will take credit for one other thing that was sort of lost in the literature. I was never convinced that HDL had a beneficial role at all. I felt that what we were seeing and in fact this is still largely true, people who have low HDL also have small HDL, triglycerides, insulin resistance and I thought low HDL was a marker and not causal. Well, this was an era where we were just starting to make transgenic mouse models and my colleague E.M. Rubin and I took a mouse model of atherosclerosis and expressed the human ApoA1 gene.

So were able to jack up the A1 levels and make human like HDL. And guess what? They had less atherosclerosis. So that actually convinced me that there is potentially an important role for this pathway if you are increasing ApoA1 availability. That's probably the best way to reduce risk from the standpoint of HDL raising and maybe measuring ApoA1 is a good reflection of that, but it's really the dynamics, it's the production.

So that's been a holy Grail in the Pharma which has not yet yielded a drug that has that effect. So it's still I think kind of undeveloped as a potential path to be able to pinpoint what it is that reflects that quality. It's doable, we just haven't gotten the answer yet.

Bret: So it seems like it's clear that a low level is an increased risk factor based on Framingham data, based on all the observational data we have that actually a low level of HDL is a better predictor than a high level of LDL but maybe the higher level of HDL, there's some sort of subset and differentiation we still need to make.

Ronald: Yeah, but a low level of HDL is a risk factor, I'll come back to the point, that when you start introducing measurements of small LDL for example, remnant lipoproteins, which is another class of triglyceride particles that are atherogenic, high levels of those particles tend to travel with low levels of HDL.

So again we don't know how much of the risk that is attributed to low HDL is due specifically to low HDL, something probably is, but a lot of it may be related to the co-conspirators that are part of this syndrome, the metabolic syndrome.

Bret: Which brings us back to these low-carb hyperresponders with naturally high HDLs in the 80s and 90s, naturally low triglycerides in the 40s, 50s and 60s and then the LDL cholesterol above 200, the LDL-Ps in the 2000 range and... it is unchartered territory with, you know, things coming from both sides.

Ronald: If we have a conversation maybe two years from now, maybe we will have completed a study that I've been really anxious to do and in fact I am talking about developing, where we at least look at the cause of that hyper response. Is it production, is it clearance? This is in fact the residence time in which these particles are just sailing through and causing problems. Maybe they're going the other way, maybe they're coming back.

Bret: Right.

Ronald: But these are all kinds of questions that have been out there which had been more or less pure fantasy because we don't have the data. So I think it's one of the more interesting questions that I'd like to address.

But having said that, I think as we talked about a moment ago, there is a subset of individuals who have this trait who for all intents and purposes look like they're not going to develop coronary disease at least over the short-term data, no family history, there's nothing else genetically going on... And this high LDL-P response may be benign in a subset of those individuals. We just need to know they are.

Bret: Right. One thing that's so interesting is a number of physicians when they see these people they want to label them as having familial hypercholesterolemia and throw them on a statin right away. And that shows the failings of just wanting to hang your hat on one biomarker instead of realizing FH is a is a constellation of symptoms, diagnosis, family history and physical exam findings.

Ronald: That's one interesting feature. If you have one of the FH genes, if you're heterozygous for FH, you may go through life with high LDLs and never have any problems at all. There are families like that. And so it's not always a marker for high risk.

Homozygous FH, where you have two genes and you have super high LDLs, that I think is a different category. But there are people who-- It gets back to your point, just based on the LDL alone, even in those patients may not be sufficient for assessing the risk.

Bret: So how else would you assess the risk? Would you use calcium scores, CMT... what other tools do you have in your toolbox?

Ronald: Well, calcium scores I do use in situations like that. I don't use them a lot routinely, but if there's any question that a patient presents, either genetically or on a low-carb diet with a high LDL-P and with what looks like an otherwise metabolic profile, I do use a calcium score as a way of helping me to stratify risk, because sometimes there's some people who do have some calcium, in those I go after it.

If they don't, it doesn't necessarily give them a clean bill, because after all the calcium score is just measuring the outcome of a plaque that may have already healed. It's not measuring the cholesterol in other parts of vessels that are parts of plaques that could become inflamed and rupture. So it is not a perfect test in that regard.

But if there is a negative family history and you can look at triglyceride and HDL small particles, if none of those things apply, it gives me much more confidence to agree with a patient who usually is coming in saying, "I don't want to take a statin." They come in and say, "I'm ready to take a statin. I'm interested in taking a statin." I usually don't argue against that, honestly because I can't be convinced that is safe that they don't need something.

But if I feel that I could support the patients to avoid statins-- Particularly, for example in young women whose absolute risk is so low to start with, I just worry about that because one of the things, and I don't want to over emphasize this because it sometimes can be blown out of proportion, but my major NIH grant right now is to address the basis for adverse effects of statins.

So we're studying the mechanisms by which statins can promote muscle damage, myopathy, as well as increased blood sugar levels and increase insulin sensitivity and diabetes. These effects tend to be written off by many cardiologists who say, "The benefit is so great that this effects are not worth worrying about."

But if you take an individual whose risk is already low and who is not necessarily likely to get a huge benefit of statin, like again a young woman and we know that the risk of developing diabetes is actually higher in women than men we may be tipping that person into a worse metabolic state by prescribing statins. I don't want to over emphasize that because people are scared of statins.

This is still a minority of the population, but we like to find ways of identifying people who are susceptible to those effects so we can advise them in advance. That's another goal that eventually could lead to better personalize medicine.

Bret: Yeah, such an important statement about weighing the risks and the benefits and you made a comment that so many physicians say, "The benefits are so great you should just take it." Well, are the benefits that great? Because that's when we get into the relative versus absolute and what baseline risk are we starting at?

Ronald: That's right, the patient population matters a lot. I think there's no doubt that for patients who have had cardiovascular events that the clinical trials strongly support the benefit of statins use. It's this sort of intermediate group that looks like they may be at high risk or borderline risk, who have not yet had any cardiovascular

events, that create the quandary for deciding is it going good be more or less harmful to prescribe statins?

Bret: That's where this CVD risk calculator comes into play, where you type in their age, whether they have hypertension, diabetes and what their LDL and HDL are and it spits out a number and based on that number you're supposed to treat. But it doesn't involve inflammatory markers, it doesn't involve any of the more advanced testing you talked about, whether ApoB or small density or LP(a). It doesn't involve any of that. It doesn't even involve triglycerides.

Ronald: Yeah, and it has a wide margin around it. So again this is the product of the role of epidemiology and public health which likes to look at population data and give numbers that apply to populations, but that population-based risk assessment has a wide variation around it and if you're dealing with smaller and smaller numbers of individuals and if you go doing an N of 1, you don't know where you are on that. So I am not a huge fan... I mean I endorsed thinking about absolute risk, but I try to integrate more than just the standard test.

Bret: Yeah, it makes sense. Dr. Krauss, I think I can speak with you for hours about lipids, this is fantastic, if I knew I have to get you downstairs here. So tell us what's on the horizon for you and where can people learn more about you and your work?

Ronald: I do have a website which is reachable through Children's Hospital research Institute at UCSF actually I have an appointment there. So people can find what my laboratory does and the kinds of papers that I've been involved with. That's probably the best way. I get people who hear about me through the social media and they find me and my web, so that works pretty well.

Bret: Okay, very good. Thank you for taking the time today, it's been a pleasure.