DANNY LENNON: Samia, thank you so much for joining me on the podcast.

SAMIA MORA: Thank you Danny, it's my pleasure.

DANNY LENNON: Yeah, we have so much that I want to get into and this is a topic that I find absolutely fascinating, and some of your research papers and publications in this area have been extremely informative and helpful to me, someone that's looking at this just with an outside interest in methodologies. So I'm keen to get into some of those specifics, but maybe just to give people some context about you and the work you do, how would you generally introduce yourself in terms of your work and your interests?

SAMIA MORA: Yes Danny, so I'm a cardiologist at the Brigham and Women's Hospital which is part of Harvard Medical School in Boston, Massachusetts. I also have advanced training in epidemiology, and my focus of research is on cardiovascular prevention, including epidemiology as well as clinical trials for prevention of cardiovascular disease, so I'm both a clinician and a researcher at the same time.

DANNY LENNON: So I think where I wanted to start much of this was looking at the general processes around atherosclerosis development when we're looking at cardiovascular disease risk in general, and then maybe we'll also look at the specific role of various lipoproteins and different testing that goes on. So maybe as a start point here, I thought it might be useful if we outline to people, when it comes to lipoproteins, what exactly are we talking about here, what are the types of maybe those various lipoproteins and then from there we can get into some of their roles afterwards, but how would we generally introduce that topic?

SAMIA MORA: So first I think the distinction should be made between lipids and lipoproteins, and the analogy I usually use is lipids which are, for example, cholesterol or triglycerides, are components of the lipoproteins. The lipoproteins are the ship if you want that is carrying the cargo and the cargo is the lipids and the lipoproteins are the carrier of the lipids. So the lipoproteins actually include lipids but they also carry other things, for example, proteins; they carry apolipoproteins, they also carry many other things that seem to also have functional relevance, so they are more complicated than the lipids. And when we talk about lipids, mostly we're talking for clinical practice, the standard lipid testing which is total cholesterol calculation for LDL cholesterol is the most common way to assess LDL cholesterol than HDL cholesterol and triglycerides. These are what we usually refer to when we say lipids versus lipoproteins include particles across the size range so these are chylomicrons, chylomicron remnants, VLDL, very low-density lipoproteins, intermediate density lipoproteins, IDL, and then low density lipoproteins, high density lipoproteins, HDLs, and then other particles such as lipoprotein which is a type of LDL particle. So lipoproteins is sort of a more general way of thinking about things, and the reason we are – recently, over the past, I would say, 10 years, the focus has become more on lipoproteins because we've

realized that lipids are only part of the story, not the whole story.

DANNY LENNON: I think a really clear example that you've just touched on that will be useful for people is when we're looking at that difference between lipoproteins and let's say the lipid content of those lipoproteins. A lot of the times people will use the term, let's say, LDL interchangeably with LDL cholesterol which they may see on a lipid panel. Can you maybe just use that example as an explanation for people between the difference, between the actual particle, and the content?

SAMIA MORA: Yeah, that's a very good point Danny, I'm glad you brought it up. In fact, many cardiologists even and even sometimes lipid experts use the terms interchangeably because – so basically, what happened is a few decades ago with the National Cholesterol Education Program in the United States and many other countries also, we started recognizing that cholesterol is one measure of cardiovascular risk based on very old data from Framingham Heart Study and many other studies worldwide. There's been an emphasis on cholesterol, so the trend has been over the past few decades to measure cholesterol because that was something that we could measure. Now, when people say LDL they really refer to, in general, LDL cholesterol. But it turns out, as I said, the lipoprotein is a particle like a ship that's carrying the cholesterol, it also carries triglycerides. So the LDL particle has LDL cholesterol in it as two components – actually, there's a little bit of the free cholesterol on the outside surface of the particle and then inside is where most of the cholesterol ester core is, and that's where most of the LDL cholesterol is being carried inside the particle. And actually, the reason you need a particle is because you can't just have the triglyceride and cholesterol ester just floating freely because it's hydrophobic.

So you need something that carries it in the bloodstream, so these lipoproteins carry the

lipid. Now, when people say LDL cholesterol, again they usually – it's that one component, but the LDL particle includes these other things, for example, it includes Apolipoprotein B Apo B. It also includes phospholipids on the outer surface and includes sugar particles, etc., so it's a more complicated particle. And we've recently realized there's many aspects to LDL, it's kind of looking at an elephant and saying, well, there's the ear and there's the tail. And if you just touch the elephant in one area, you'll only see that part of the elephant but you really ideally would like to see the whole elephant. And that's not just for LDL but in fact we like to do it for all the particles, so LDL particle usually refers to the entire particle, and then people have different ways of measuring that, for example, the size of the particle, you can measure how big is the particle, and usually bigger particles carry more of that core across or more of the core triglycerides, so the bigger particles generally have more cholesterol in the middle.

You can also measure the number of these particles, and the number of these particles really is a concentration, because in the blood you have fluid and so you have these particles, and if you have more of them, you have a higher concentration. So that's what we mean by number, and that usually is the LDL-P or LDL particle number which differs from the LDL cholesterol which is the cholesterol carried by these LDL particles in total. There are other aspects again of LDL, people are doing now even more proteomic and other aspects lipidomic analysis of the particles, and those are still emerging. But for example apolipoproteins, there's a lot of interest in the apolipoproteins being carried by the LDL. So some of these particles carry Apo C3 on the surface, not all the LDL particles carry them, but many of them do, and those do seem to also have increased risk. So there's a lot of nuance to the LDL more than just the cholesterol.

DANNY LENNON: Yeah, and I think definitely, later when we discuss, maybe some of the markers that can be used to assess risk, we'll look at these various different components of either measuring that particle number or their actual lipid content, so to speak.

SAMIA MORA: Yes, and also Danny, to keep in mind, because many people don't know this that LDL cholesterol and even HDL cholesterol, these are operational definitions. So if you told me come up with some definition of LDL cholesterol, it's really not based on any unique characteristic of the particle, because it's a spectrum. So these lipoproteins are a spectrum, and I think that's part of the confusion is that there are many of them and then there are so many, and then people just sort of at some point get confused. But it turns out that the reason, the way it was even defined, it was an operational definition based on ultracentrifugation which was the first method developed to measure cholesterol. So you take the blood and you spin it and the stuff that comes down, the stuff at the very bottom is the HDL, and the stuff above that is the LDL. So it was really an operational definition and they defined, you know, this was the National Laboratory Network, CDC reference method is basically just an operational definition as the cholesterol that's at a certain density – the density more than 1.006 when you centrifuge it at a certain speed, etc. So it was really an operational definition.

And in fact, clinically, we often do not measure LDL cholesterol, we calculate it, and it's sort of a subtraction, it's what's left over when you remove the VLDL which is a triglyceride predominantly, and you remove the HDL, and most of what's left is the LDL, so that's called the Friedewald calculation and there are other methods now also for calculating that or improvements on the Friedewald. But basically, it's an operational definition, not really like there's anything distinct about this

particle that makes it LDL and not IDL for example or another particle along the range.

DANNY LENNON: Maybe a good start point before we start discussing some of those various different markers we could look at, is just to get everyone on the same page when it comes to atherosclerosis development and why we're even talking about lipoproteins and lipids in the first place – what is it about lipoproteins and how they are implicated in atherosclerosis development that makes it of interest to us in the first place?

SAMIA MORA: Right, so cardiovascular disease clinically manifests usually at older ages, so for most people it manifests for men in their 60s and women in their 70s, clinically, as a heart attack or a stroke, or even sudden death. But it turns out that the development of atherosclerosis, meaning the plaque becoming abnormal in our arteries actually starts at a very, very young age. In fact, the Bogalusa Heart Study was one of the first that showed that even young kids, people between the age of two and 20 already have the beginnings of atherosclerosis in their arteries, and these were people who died from other causes such as accidents when they did their pathology.

So basically, the process is a very long process, and that's part of the challenge, but also part of the reason why we can also intervene earlier and prevent it. So it was recognized a long time ago, around the time of the Framingham Heart Study and the time that they were starting to measure cholesterol was that countries that had high cholesterol seemed to have higher risk of cardiovascular disease, especially coronary heart disease. And there was also noted that that risk could be assessed with a test that was, at the time they would measure total cholesterol and HDL cholesterol and HDL cholesterol is inversely related to risk and total cholesterol is positively related to risk, and they put those two in even the earlier models that predicted cardiovascular disease and they

found that they're very good predictors of cardiovascular disease. So for one thing, it predicted cardiovascular disease, and then at the same time all the basic science and the biology, all the studies that were experimental studies being conducted showing that LDL receptor and then the LDL particles are actually causing atherosclerosis, so they're not just a marker of risk but it's actually causal, it's involved in the development of the plaque.

And that is a whole basis for why we look at them clinically. Now, does it tell you the whole story? It turns out no, it does not tell you the whole story. So just knowing your total cholesterol or LDL cholesterol or HDL cholesterol doesn't actually tell me for sure you will or will not develop cardiovascular disease clinically over your lifetime. But it definitely gives me a better assessment of your risk, especially when taken in combination with other risk factors. We also know that the lifetime exposure to having high LDL cholesterol, high LDL particles in your bloodstream is also substantially related to risk. So people who have the genetic dyslipidemias, like people such as familial hypercholesterolemia, etc., these people are exposed to very high levels of atherogenic LDL particles and some of those other particles like LPA, and those people tend to have cardiovascular disease at a younger age. The other people tending to have cardiovascular diseases at a younger age, even if they don't have a high LDL cholesterol or people who have high LDL particles but were not picking up on the fact that they have high LDL particles, and I'm sure we'll talk about that a little bit later today.

DANNY LENNON: Yeah, I think one of the really important points just to clarify on what you've just said Samia that when we're looking at these atherogenic lipoproteins, it's not just some sort of correlation for risk, we're seeing that there's a causative role here, so not necessarily that the presence of them alone guarantees

cardiovascular disease, but rather that we need them there in order for that development to happen.

SAMIA MORA: Correct, and that causal role turns out to be for the LDL particles and hence the LDL cholesterol because these particles cross the endothelial barrier in the bloodstream and they actually go into the plaque and help the development of the plaque after they get oxidized or modified in some way. And then also, it turned out more recently, we've identified that there's also a causal link for the triglyceride rich lipoproteins, these are what we call the remnant particles, the LDL particles or remnant particles that also, once they become small enough to also cross that endothelial barrier, can also be causally related to cardiovascular disease. And a lot of recent studies with causality linked the genetics with the clinical outcomes and that has been really also very valuable to see which pathways seem to be more related to risk. And then the key thing is also that we have therapies to intervene, so if we didn't have any therapies, we could be arguing about this all day. But the great thing is we have ways to intervene whether lifestyle, whether medications to actually reduce the risk.

DANNY LENNON: Right, so based on some of what you just said, one of those important aspects of these atherogenic particles is that there's an ability for them first to be able to penetrate that arterial wall and get in below that layer, that again may correlate back to size, and you just mentioned that if there may be too large of a particle that may not happen. So first of all, which of those previously mentioned particles that we've discussed do have the ability to penetrate the arterial wall – and then beyond that, how do we distinguish between those various different particles we've already mentioned, which ones are pro atherogenic and which ones are not?

SAMIA MORA: Yeah, so it turns out that it's actually a very easy mnemonic to remember which ones are the bad ones. So the ones which are bad, and I remember there's B for bad, are the ones that are Apo B carrying. So I remember Apo B, B is bad. These are the ones that that are atherogenic. So any particle that's carrying Apo B, turns out, they have a lot of data supporting that these are atherogenic bad particles for you. So all the LDL particles, whether they're smaller or medium or large size, all the LDL particles are atherogenic in terms of they've been related to cardiovascular risk and there's also basic science data that they actually also participate causally in the process of atherosclerosis.

For the larger particles, so now you're talking about other kinds of particles, so for example, the LDL particles, very low-density lipoprotein particles and what we call chylomicron remnants, so the remnants is because the very, very largest size particles which are the chylomicrons which are the particles that we produce after eating, these ones are so big that they cannot cross the endothelial barrier. But once you get to the remnants, they get smaller and smaller as they release the triglycerides and those particles, for example, chylomicron remnants or VLDL particles – again there's a lot of data recently emerged that these are also causally related and can cross the endothelial barrier, there's a lot of debate as to is the causality because of the cholesterol they're carrying or the triglycerides they're carrying and which one is more important, but I think it's almost like sort of the particle carries both the triglyceride and cholesterol.

Now, there are other types of particles that are, for example, Lp(a)-which is an LDL like particle, it's not LDL, but it has similarities with LDL, that also turns out to be atherogenic and that also carries Apo B. So all of those that are atherogenic carry Apo B. HDL particles are not thought to be in general atherogenic. HDL is a very confusing particle because it has

many, many functions and many roles, so we're still learning a lot, but HDL carries Apo A. So the simplified version would be the Apo B carrying particles such as LDL or IDL or VLDL or chylomicron remnants or atherogenic or LPA, whereas the HDL carrying particles carry Apo A, and those, it depends, there's a lot of nuance there, so some of them may be atherogenic but in general, at least, in terms of cardiovascular risk the association is inverse in terms of cardiovascular risk, but there's a lot more controversy about the exact roles of HDL.

DANNY LENNON: So we have this set of different particles and some of those you mentioned LDL, IDL, the VLDL, chylomicron remnants, Lp(a), these are all essentially atherogenic and their ability to kind of penetrate the arterial wall.

SAMIA MORA: Right, so that's why people have now more recently, like over the past probably 10 years or so, been emphasizing non-HDL cholesterol, because non-HDL cholesterol is basically the cholesterol carried by all these Apo B carrying particle, excluding the HDL. And so all the atherogenic lipoproteins carry the cholesterol and that is referred to as non-HDL cholesterol. Now, if you measure the number of these particles, that would be reflected in Apo B, because as I said, Apo B is carried on each particle, and it turns out lucky for us is that each particle that's atherogenic carries only one Apo B. So since each one carries only one, then we know that there's a direct proportionality in terms of, if you have a higher Apo B, you have more of these bad Apo B carrying particles. So Apo B really identifies a number of these atherogenic particles versus non-HDL cholesterol tells you how much of them are carrying cholesterol. So non-HDL cholesterol equivalent for Apo B, similar to how LDL cholesterol is the cholesterol equivalent to LDL-P.

DANNY LENNON: Okay, perfect. I think that's a really useful way for people to think of it that we have these two measures, one is measuring that cholesterol

content of these certain particles and then there's other measure, well, it's measuring the number of those particles. And I think that's a perfect segue for discussing these various markers for risk because quite conventionally and even still to this point now, as we've already alluded to, and a typical standard lipid panel that someone may go as part of their ongoing routine testing with their doctor for example, that main lipid panel would, particularly at least couple of the markers that are often looked at would be things like total cholesterol, the LDL cholesterol and so on, as markers that would signify some degree of risk. So based on what we've said, if we start working through some of those various different markers, is there still a useful role in risk prediction for something, let's say, like total cholesterol, first of all – and then even beyond that for LDL cholesterol given what we've discussed about the nuances when it comes to particle number as well?

SAMIA MORA: Yes, so in terms of cardiovascular risk, definitely, I mean, the total cholesterol, LDL cholesterol, non-HDL cholesterol, the ratio of total over HDL cholesterol, even remnant cholesterol, these are all related to increased cardiovascular risk. Now, then it gets in turn the nuances of, okay, well, if you have a high cholesterol, let's say, total cholesterol, well, that could be contributed to by the atherogenic parts, for example, the LDL or the IDL, VLDL cholesterol, or it could be contributed to by the HDL. So since the HDL in general for risk prediction is inversely related, it doesn't mean in every single person who has a high HDL is protected. But if you took populations of people that have higher HDL, they tend to have a lower risk than people at lower HDL.

So if you just looked at the total cholesterol, you wouldn't know how much of that is from the HDL versus the Apo B or atherogenic particle cholesterol. So that's why if you did the non-HDL cholesterol, it often tells you in population studies, better information than

just the total cholesterol because non-HDL cholesterol is really zooming in on all the atherogenic particles. So compared to LDL cholesterol, LDL cholesterol also carries increased risk but non-HDL cholesterol seems to be better, especially in populations that have greater or people who have greater levels of the remnant cholesterol or the VLDL cholesterol, because as we said, those are not captured by LDL cholesterol. So if you wanted one single measure that really identifies your risk, if you had to only check one, from the standard lipid profile, the non-HDL cholesterol would be better than the total or the LDL cholesterol because it gives you as a summary measure.

Now, I've also used total cholesterol over HDL cholesterol ratio and that actually turns out to be a very good predictor of risk as well, but the only problem with that issue to recognize is if somebody has a very high HDL cholesterol, they're not always protected against cardiovascular disease. And so while this is a good marker, the HDL component is more complicated. Now, it turns out, if people have high LDL cholesterol or high non-HDL cholesterol, well, they're definitely at increased risk and they should reduce their LDL cholesterol or non-HDL cholesterol in ways to reduce their risk. So in those people checking in Apo B is not always very informative, it could be informative in a small subset, but in general, because you already know they have high cholesterol, so they should reduce it. The way these other Apo B measures come in handy is for people who already have say either average LDL or average total cholesterol or non-HDL cholesterol or had even low levels of those, because you would think that once you get the cholesterol to a low enough level, people don't have cardiovascular events clinically. It turns out that's not the case. In fact, over the past few decades, we've had reductions in LDL cholesterol and total cholesterol in Western populations and some of that is related to statins but not all of it. But at the same time people are still having heart attacks and strokes

and clinical cardiovascular disease events, and that's where the Apo B can come in handy, because then the Apo B which is the number of particles, can tell me, oh this person has a high risk because their Apo B is still high even though their cholesterol is low. And so that's where I think the key role for Apo B or other particle measures can come in.

DANNY LENNON: Yeah, and this is such a crucial point because, like you say, when some of this data starts to emerge of, hey, look we can point to people who have a "normal" LDL cholesterol or normal non-HDL cholesterol, and that still end up getting cardiovascular events and sometimes that type of data gets jumped on by, let's say, the LDL deniers that want to presume that everything is – there's just no connection here, and so look, it doesn't make sense, we don't need to worry about this LDL stuff at all – whereas in reality what's really going on is what some of your publications have been incredibly informative for me is discussing these ideas of concordance and discordance between some of those markers which you've just alluded to.

SAMIA MORA: Yeah, and the way that happens Danny is basically people who have "normal" LDL cholesterol or low LDL cholesterol, it could be that they have that because they have few LDL particles or few of these atherogenic particles, but it also could be that they have many of them but that they're small in size and they carry less cholesterol – remember, how at the beginning of the conversation we talked about the bigger the LDL particle, the more cholesterol it carries. So you could have two LDL particles side by side and one is very big, carries a lot of cholesterol, the other one is very small and carries only a small amount of cholesterol. And if you had many of the big ones your cholesterol would be very high, these are the FH patients, familial hypercholesterolemia, they have a lot of LDL particles and they have a lot of cholesterol per particle.

But then you have some people on the other extreme where they have small sized LDL particles that carry only a small amount of cholesterol per particle but they have many of them. These are the people with diabetes, metabolic syndrome, obesity, the unhealthy obesity syndromes like insulin resistance, people have high triglycerides, these people, and unfortunately over the past few decades we are really facing a huge epidemic of diabetes and obesity worldwide, those types of people may kind of be deluded into thinking their cholesterol is normal, because it's not showing up on the standard test because the LDL cholesterol when you check it in these people it's actually not elevated or even low. But it turns out, if you did another test such as Apo B or the LDL particle number, you'll find that they have many of these particles even though they're small in size. And since it's really the number of particles that's causing the atherosclerosis, these people are also at increased cardiovascular risk but they're not picking it up from the standard lipid test. Now, the ideal situation you want to be in is you want to have few LDL particles or a few atherogenic Apo B carrying particles, so you want to have a low Apo B or a low LDL cholesterol, low non-HDL cholesterol, and you want to have a low number of particles which you would only know about if you checked in Apo B or a particle, you know, another test that tells you about the particle count because it's hard to estimate it from the standard lipid profile.

DANNY LENNON: Right, and I think this is just so crucial I think just to really make this clear on what you've just laid out for us Samia is we could have a situation where, let's say, we take two hypothetical people and they have the exact same LDL cholesterol number, and that would fall within, let's say, the normal range. It could be conceivable, if we take an extreme example, for one of them to have a relatively low number of LDL particles carrying that cholesterol around, and we can have someone else who has

a large number of these particles carrying that same total number of cholesterol because there's relatively small amounts of cholesterol in each one of those particles. And so the actual particle number is very different in those two situations which means there's vastly different risk profiles for each of those hypothetical people despite having the same LDL cholesterol number.

SAMIA MORA: Absolutely, that's exactly – and unfortunately, this is not a hypothetical situation, it happens a lot, it turns out in generally healthy populations, this, what we're calling this, discordance, meaning there's disagreement between the cholesterol and the number of particles with Apo B measurements, actually is about 20-25% of the population, but in populations that are enriched with obesity or insulin resistance or metabolic syndrome, hypertriglyceridemia, these actually can be many – a large proportion of the population, could be even 30 or even 40% of the population. So we're missing these people because we're not even capturing them, we don't think there's even a cholesterol problem. Even though they really do have a problem, it's a lipoprotein problem, not really a cholesterol problem, but they do have a lipoprotein problem.

DANNY LENNON: So we have both probably at some genetic level just as into individual variation and the likelihood of someone having concordance or discordance between, let's say, that LDL cholesterol and LDL particle number or LDL cholesterol and Apo B particles?

SAMIA MORA: Yeah, there's definitely a genetic component, it's multifactorial but there's also a lot of lifestyle influence, especially obesity, especially the abdominal obesity, the central obesity, the insulin resistance syndromes, basically the diet and lifestyle can have huge effects on this particular problem. And there could be also genetic components – for example, people have familial combined hyperlipidemia, they would

have higher levels of both the VLDL and the LDL particles, but you may not even think, you may not even capture it with necessarily the standard lipid profile. So again, these people, yes absolutely, this is an important issue, and the way to recognize these people is actually by measuring an Apo B which is a simple test, it's almost available in any hospital, it's a chemical assay. It's been standardized recently and that's why we weren't using it before so much because it wasn't standardized. But recently, it's been standardized, so you can be confident that the result is as long as the assay and the lab being used is standardized, and the nice thing there is I can tell you exactly what is measuring versus when you asked me at the beginning what is LDL cholesterol. Well, what makes an LDL particle an LDL particle – that's a much more philosophical question. But Apo B, I can tell you exactly what it is, it's this apolipoprotein, you can actually target it with an immunoassay, or other forms of measuring it, so basically you know exactly what you're measuring.

LDL-P which is LDL particle number, basically Apo B is the total number of these atherogenic particles. In most people, over 90% of the Apo B is actually from the LDL particles, so in most people Apo B is basically affecting LDL particle number. And some people who have a lot of the VLDLs or chylomicron remnants have a lot of remnant particles, in those people the LDL particle number would be different from their Apo B because they have a lot more contribution from the other atherogenic lipoproteins such as IDL or VLDL or chylomicron remnant particles. And in those people, the Apo B is not corresponding very closely to the LDL particle number, but in most people the vast majority of people, Apo B is basically an estimate of the LDL particle because they're the most common type of atherogenic particle in the bloodstream.

DANNY LENNON: So when it comes to potential testing to assess risk, and again this could be an oversimplified

question, could be opening a can of worms, but would an Apo B test be the most informative for a given individual person, let's say, rather than other testing or does a standard lipid panel still tell us enough of what we need to know initially, or how should people wrap their head around what is the best port of call for testing to assess risk?

SAMIA MORA: Yeah. Well, if you had to pick one, I would pick the Apo B, but the reality is that everybody gets a standard lipid test, because that's how the cholesterol measurements happened before the Apo B measurement just historically. So if we were back to rewrite history and now we have Apo B and the cholesterol test, we would of course be teaching everybody about Apo B. But that's not how history happened, it happened that we actually could measure cholesterol first, and everybody is very familiar with the standard lipid profile – so I think standard lipid profile tells you a lot, it doesn't tell you the whole picture. So if you really want to know the whole picture, I would recommend, and many societies are now moving to that, and actually the European Atherosclerosis Society, the European federation for laboratory medicine and clinical chemistry, we worked together for several years on a consensus based recommendation as to which of these should we measure, and the consensus of this panel of experts from many European and international countries was, okay, well, use LDL cholesterol and non-HDL cholesterol as the primary targets, but then also check an Apo B, and also check an Lp(a), and those can be, you know, Lp(a), the levels in general don't change that much, so you could just do a onetime measurement, and Apo B could be especially useful in the discordant people, but you wouldn't know that you're discordant if you didn't check it, so that's why, and it's a pretty cheap assay. So I think for people who really want about their lipid or lipoprotein related risk they should check both the standard lipid panel, calculate the non-HDL cholesterol because it's not always reported so that would

be total minus HDL cholesterol because that's the bad atherogenic cholesterol, but check an Apo B, because that tells you about the number of particles, and then check an Lp(a) because that also is hard to sometimes identify from the standard lipid panel, and that could also be a genetic component, LP(a) is mostly a genetic component, so you can just check it once and if it's low, you don't have to worry about it.

DANNY LENNON: Yeah, I think that's a really important point because I think the tendency or the trap we could fall into is as we learn about the value of something like an Apo B test is to think that all other previous markers that we could use are now irrelevant, whereas really that's not what is being said, it's that this gives us an added layer of our ability to dial down and be more exact and more accurate with evaluating risk, but we still have that value from the others.

SAMIA MORA: Yes, because, for example, the people at the most risk are actually people such as patients who have familial hypercholesterolemia, because these patients have both high Apo B and high cholesterol. So the people at the greatest risk are those who have both elevated, the LDL cholesterol is high or the non-HDL cholesterol is high as well as the Apo B, because they have many particles and they're carrying a lot of cholesterol. The people who are at the lowest risk are the people who have few Apo B or few particles and few, you know, little cholesterol carried by them. And then the trick becomes the ones in between, the trick becomes if you just did the standard lipid profile, you'll capture the ones in between who have the high LDL or high non-HDL cholesterol, but you won't pick up those that have the high Apo B even though their cholesterol is not elevated. And that's the population that we call discordant, and these patients typically again have a lot of metabolic abnormalities, they may have slightly elevated triglycerides, they may have even mildly elevated, could be in the range of 1.8 millimole per liter or 175 milligrams per deciliter if it's

non-fasting or slightly, you know, in that 150 milligrams per deciliter range for fasting, or they could have diabetes or prediabetes metabolic syndrome, even obesity. So these are the patients who should get that task, because if you do get it and it's high then you should be more aggressive about reducing the number of particles.

DANNY LENNON: So in terms of either preventing or even treating a phenotype that, let's say, would carry a high risk and we've talked about, for example, the high number of atherogenic lipoproteins, putting someone at high risk, is there a certain set of characteristics related to diet that typically leads to that more undesirable phenotype of this high atherogenic lipoprotein load, what are the things that we know at least with the connection with diet, and again, I realize this could probably be a whole conversation itself, but what are kind of some of the overview levels stuff that we are fairly sure of right now?

SAMIA MORA: Okay, so for diet, I would say, the key thing with diet is look at which diets have been shown to reduce clinical events, so which diets have been shown to reduce heart attack and stroke. Because while I love lipids and I love lipoproteins, and we can talk about them forever, but they're still surrogate markers, so what you really want to know is will this person, will I, will you, will your father or mother or sister or brother or friend, develop cardiovascular disease in their lifetime, and especially if they have it early or if they have a more severe form of it such as southern death. So it turns out the only diet, and this is the only diet that has been shown to reduce clinical events, reduce heart attack, reduce stroke, is actually the Mediterranean diet, and it's actually the number one diet recommended in the US. Now, there are other healthy types of diets similar to Mediterranean, for example, the DASH like diet, it has some similarities to Mediterranean, but it's actually a low-fat diet compared to Mediterranean diet which is a

moderate fat. But DASH diet reduces blood pressure which is great, but has not been tested for clinical events, although reductions in blood pressure are great, and I'm sure would translate into reduction in stroke. But again, we don't have the data for that.

So really the only diet that has – we have actually two large clinical trials that tested it in a randomized fashion is the Mediterranean diet. So that's why the strongest recommendation is for that, because the other diets have effects on lipids and lipoproteins, as does the Mediterranean diet, but it turns out the Mediterranean diet doesn't really affect so much the level of the cholesterol or the level of these particles, but it does affect how they function. So it's very complex, lipoproteins are not just these particles just carrying the cholesterol or triglycerides but they actually have also functions, and so it turns out that the Mediterranean diet has beneficial effects on the functional aspects of the lipoproteins even though it does not affect so much the absolute level. So if you went on a Mediterranean diet without losing weight, then you would probably still have the same level of cholesterol. But we know that just by going on that diet, you will likely reduce your risk at least from the studies we know by about 30% at least, including reductions in sudden cardiac death.

So diet is complicated. I would say, for a diet, I would really favor, and that's what I recommend to my patients, to everyone, because we really need studies to assess is that diet beneficial for you or is it just causing something like weight loss but then maybe even though it may cause you short term weight loss such as the other diet, such as Atkins diet, but the long-term effects could be actually detrimental and it may actually increase your risk for other clinically relevant things. So yes, so for diet, I would say, focus more on the overall dietary pattern, and not so much these fad diets that restrict things

extremely in some way or another, and then we don't know the long term side effects.

DANNY LENNON: Right, yeah, and I'm so glad that you mentioned that kind of important distinction of we can look at the impact of diet on lipids per se, but it's also kind of a separate conversation to look at the impact of dietary patterns overall on actual cardiovascular disease outcomes, and they're kind of slightly two separate conversations, although related, so I think that's an important point to bear in mind. We're coming just up on time here Samia, and I could stay going for hours more if I could, there's so much that I could have asked you about related to things like statins or Lp(a) that we could go on forever about, so maybe for another time. But for today, before we start wrapping up, for people listening that want to go more in-depth in this area, for example, a lot of people listening are maybe doctors, GPs, family physicians and so on or others who just have an interest in the pathology and nerding into the little details of that we've just scratched the surface on, are there any particular papers or resources that you direct their attention to if this is an area of interest?

SAMIA MORA: Yes, I think the European Atherosclerosis Society consensus documents, we've actually just put out recently in clinical chemistry laboratory medicine a synopsis of it. It was published about a year ago in clinical chemistry and it's been adopted sort of into some of the other international guidelines. I think that one has the most comprehensive, it's called Quantifying Atherogenic Lipoproteins for Lipid Lowering, and I can send you that reference. It turns out, actually, I'm in the process now of revising the Braunwald Heart Disease chapter, I'll give here a plug-in for my future chapter which should be coming out in the next year or so, the Braunwald Heart Disease chapter on cholesterol. I would be actually working on that as well so that could be a nice reference, but I think the European Atherosclerosis Society summary paper goes into a lot of detail about

that. If that's too much detail, then I would recommend a shorter version that I basically wrote about maybe a few years ago that gives you some of the descriptions for this discordance, and that was in circulation about two years or a year or two ago, it was an editorial, I can give you that reference as well.

DANNY LENNON: And so with that that brings me to the final question that I always end the podcast on – and if you could advise people to do one thing each day that would have a positive impact on any area of their life, what would that one thing be?

SAMIA MORA: I would say do not underestimate lifestyle. Diet, and exercise are key. You could do small amount, you could actually do 15 minutes a day of physical activity, and if you do that every day, every day, every day, you will have substantial benefit. Small changes in your diet, in the Mediterranean diet – even if you improve your diet by two points closer to a Mediterranean type diet, you have about the same reduction in risk as like taking a statin. So I would say do not underestimate lifestyle. Now, in addition to that, we need other things, that's why medications have been developed, but do not underestimate it. Start early, start young, and maintain it – even if you can do only a small amount, that small added benefit adds up over time. So think small but maintain it, maintain it over – make it as a habit.

DANNY LENNON: Samia, thank you so much for not only the great information you've given today in this great conversation that I've really enjoyed, but for giving up your time and for the great work that you are continuing to do. It's been an absolute honor to be able to talk to you, so thank you for doing this.

SAMIA MORA: It's my sincere pleasure Danny, really enjoyed talking with you and I'm so glad there's interest in this topic that we can get the word out to people are interested in it.

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