ADAPT Interview with Dr. Peter Attia

Hello ADAPTers. I'm excited to bring you this interview with Dr. Peter Attia. Dr. Attia is the founder of Attia Medical PC, a medical practice with offices in San Diego and New York City focusing on the applied science of longevity and optimal performance. The practice applies nutrition science, lipidology, four-system endocrinology, sleep physiology, stress management, and exercise physiology to minimize the risk of chronic disease onset, while simultaneously improving healthspan.

Dr. Attia trained for five years at the Johns Hopkins Hospital in general surgery, where he was the recipient of several prestigious awards including Resident of the Year and author of a comprehensive review of general surgery. He also spent two years at NIH as a surgical oncology fellow at the National Cancer Institute, where his research focused on immune-based therapies for melanoma. He has since been mentored by some of the most experienced and innovative lipidologists, endocrinologists, gynecologists, sleep physiologists, and longevity scientists in the United States and Canada.

Dr. Attia was the founder and president of a medical research organization that funded human clinical trials in nutrition and metabolic disease. During his four years as president, they raised and deployed over $40 million.

Dr. Attia earned his M.D. from Stanford University and holds a B.Sc. in mechanical engineering and applied mathematics.

So, I've known Peter for several years. He's definitely one of the smartest people in the room in any room that I've ever been in and I've been in a lot of rooms with a lot of smart people, so that definitely says something about him. And when I think about lipidology and considered who I wanted to have as a guest expert for the ADAPT program, Peter was at the top of the list. He has trained with Dr. Tom Dayspring, who's perhaps one of the foremost experts in the world on this topic and Peter also brings a wide base of knowledge from other disciplines. He is familiar with the dietary approach that we talk about in this program and somewhat familiar with functional medicine as well. And like me, he is kind of a synthesizer and a translator of all of this information. He gets it from disparate places but puts it together in a really cohesive way.

So I asked Peter to come and talk about several topics, but particularly lipoprotein(a) as a risk factor for cardiovascular disease and then to discuss briefly some of the non-lipid biomarkers, as well as some of the non-serum markers of heart disease like calcium score and CIMT and the age-old question that we all want to know the answer to, which is, "What happens on a Paleo or lower-carb type of diet when all of the other risk factors improved but LDL-P goes up or even through the roof?" So, we're going to dive into all of those topics in considerable detail and I've also been in discussion with Dr. Attia about a future advance module on how to more thoroughly diagnose and treat these lipid abnormalities.

Okay, so without further ado, let's dive in.

Chris Kresser: Peter, thanks so much for being here. It's always a pleasure to talk with you.

Dr. Peter Attia: It's a pleasure to be here.

Chris Kresser: We have a little over an hour, and as we were discussing before we started the recording, we could probably spend an hour on every one of these topics that I want to cover with you, so with that caveat, my intention is that we can just kind of summarize some of these topics and get people a starting point because I think in many cases, this stuff is not common knowledge even amongst the cardiologists that are currently working in a conventional paradigm right now. So, just giving some awareness of these topics is a great starting place.

So, let's start with lipoprotein(a), which is a really important player in determining cardiovascular disease risk, so tell us a little bit about why that is and why this is a marker that we should all be testing for.

Dr. Attia: Well, maybe even before doing that, it might be worth explaining what it is because I've noticed that for the nomenclature around lipoproteins, it's complicated. There are a lot of terms that are used interchangeably that aren't actually interchangeable. For example, when people talk about LDL, low-density lipoprotein, you know, nine times out of 10 they're actually referring to low-density lipoprotein cholesterol content, or LDL-C, but you can also of course refer to the number of particles, and I'm sure we'll get to that distinction later on. But let's assume for the moment that the listener understands that we're talking about that, that we know that difference, so, you know these things that are low-density lipoprotein particles, of course these things exist because cholesterol cannot be trafficked in a free state because it's not soluble in water, it's sort of hydrophobic, and therefore needs to be packaged inside of this thing called the lipoprotein, which allows it to be moved back and forth in the body.

Now, this is important to understand because it explains the entire role of lipoproteins, but basically, every cell in the body makes cholesterol and most cells can actually make sufficient cholesterol to suit their own needs which primarily comes down to two things, cellular membranes and hormones. But of course, many cells cannot make sufficient amounts, and therefore, there's this traffic that exists where some cells end up exporting cholesterol, others become the importers, and then of course there is the brain which is like an island where neither imports nor exports more or less.

So, one the most important of these lipoproteins is the LDL, the low-density lipoprotein, and of course it has a bad rep for a good reason but generally the wrong understanding. So most people assume that it's the amount of cholesterol within the LDL particle that's problematic because that's what we typically measure, and while that is associated with its risk, it turns out the risk is driven more by the number of particles.

So with all that said, there's a very special type of LDL particle that is this Lp(a) that you referred to, and the Lp(a) is an LDL particle that has covalently bound to it another lipoprotein called apolipoprotein(a). So, to put this again in context, what makes an LDL particle an LDL particle is a number of things but its defining feature is its apoB, specifically, its apoB100. So if you picture a sphere, which is what these things are, they have these lipoproteins attached to them, and the

apoB, which is also attached to the LDL particle, is loosely correlated with a number of LDL particles. So now, if you picture one of those LDL particles and you tack onto it another apolipoprotein called apolipoprotein(a), that's your LDL particle.

Again, before getting into why we should care about that, it is also worth explaining a little bit about what that looks like because this becomes part of its pathology. So I'm sure some of the people listening will be familiar with plasminogen, which is a clotting factor. Plasminogen is a protein that has these five Kringle domains. So the Kringle refers to this repeat folding structure, and so it has these five Kringle domains, Kringles 1 through 5, and plasminogen of course is responsible for blood clotting. Now, apo(a) does not have the Kringles 1, 2, and 3 but it does have 4 and 5. Now, the 5 is the same as plasminogen, but the 4 is slightly different. There are actually 10 subtypes, though two of them drive the size.

Okay, might be more information that the average person wants. What you take away from that is the following: apo(a) has a very significant homology to plasminogen. And by the way, that may actually explain why it has some evolutionary advantage. It would actually be a procoagulant.

Chris Kresser: We come out of the trees, we get cut, scratched by a predator or what not, that clotting is going to save our life.

Dr. Attia: Absolutely, because the damage that Lp(a) does, which really falls into three categories, which we'll talk about, was more likely to kill you in your post-reproductive years, whereas dying from a hemorrhage could occur at any point in time, so there's certainly a reason to see why Lp(a) would exist. The second thing is that Lp(a) actually has the thing called the lysine-binding domain, and it's a scavenger for oxidized lipid moieties. Now, that was probably an advantage in an era where we were not overwhelmed with oxidation. It now turns out to be problematic for two reasons. One, we live in a highly oxidized world, and two, there's a subset of people that have a very high number of these Lp(a) particles, and it now becomes a double whammy, which we'll discuss in a moment, because now you have a carrier that is out there scavenging oxidized lipid moieties and actually delivering them with greater efficacy in the subendothelial space. And oh, by the way, it's a procoagulant so it really becomes problematic.

So, okay, with all that said, why is this a big issue? Well, it's an issue because of these three things. We see an increase in the risk of venous thromboembolism and I think we now see why, right? That makes sense based on this plasminogen homology. We see an increase in atherosclerotic disease, so heart disease and stroke, and we see an increase in aortic stenosis. The latter is not entirely clear by the way, so in other words mechanistically, it's not entirely clear, at least to me, why we see this increase in AS, but it's real. The hazard ratios vary from about 1.5 to two, and the Mendelian randomizations show us that the Lp(a) is responsible for about two-thirds of the risk of aortic stenosis.

Chris Kresser: Wow.

Dr. Attia: On the VTE side, the venous thromboembolism, the hazard ratio with Lp(a) is about three, a little more than three, and then on the cardiovascular side, there's a limit to our understanding of the quantification because all of the research has been done using Lp(a) mass,

and in a moment, I'm sure we'll talk about the limitations of using the mass of Lp(a), the cholesterol of Lp(a) with a particle number, but when you do look at the Women's Health Study and you look at the Lp(a) mass by quintiles, there's a very clear trend, which is the first, second, third, fourth quintile have a slightly increasing risk, but at the fifth quintile, it jumps enormously. So at the very least, when you use mass, which in a moment I'll explain why I think that's not the way we should be doing it, you'll get a sense of the enormous risk increase that comes from there.

The final point I'd say to your question is, the most recent estimates would suggest 7 to 8 percent of the population are walking around with a level of Lp(a) that puts them in that very dangerous range. And so, when you look at it through the lens of being on the frontline and treating patients, when you have a condition that is that prevalent, it's lucky if a week goes by that you're not going to see a patient who has this condition and therefore there's an enormous opportunity to save lives. In fact, I would argue that atherosclerotic disease in general and as it ties to this is sort of one of the lowest-hanging fruits in this respect.

Chris Kresser: Right. And of those 7 to 8 percent that have very high Lp(a) mass, probably 98 percent don't even know it, right? Hard to quantify that, but I know very few clinicians that are testing for this.

So, you hinted in your response to the last question that there are different ways of testing Lp(a) and mass, which has, I think historically up until now, been the most common way of testing is maybe not the most accurate indicator or risk that's conferred by Lp(a), so let's talk more about that.

Dr. Attia: So historically, which is to say up until about two years ago, there were really only two ways we could quantify this. There is the more common way, which is to measure the Lp(a) mass, and then there was this less common way, which I don't actually think can be done anymore, which is the Lp(a) cholesterol content and there is a lab that used to so do that and I don't think they're offering that anymore. I'm not even sure if they're around anymore. You might actually know it, Chris, but—

So, let's talk about what each of these tests are. Again, going back to the stoichiometry of this, you have an LDL particle, which means you have a lipoprotein that contains within it cholesterol, triglycerides, phospholipid, and you can count that particle. You can measure the amount of cholesterol in it or you can measure the mass of apoB, and similarly, you can do the same thing with apo(a), which is, you can look at the amount of cholesterol contained within the LDL particles which happen to have apo(a)'s on them and that's what LDL-C measured—I think for the purposes of this discussion, it's not really worth discussing any longer because it doesn't exist, it turned out to be a better predictor of—it turned out to correlate more strongly with Lp(a) particle member than mass did, but by explaining what mass did, I think people will understand the limitations of it. The Lp(a) mass measures the mass of all particles to which apo(a) is bound to. It's very important for someone to understand what that implies. The implication there is, I have a whole bunch of lipoproteins, some of them have apo(a)'s on them, some of them do not. I have a technique to assess the mass of the Lp(a) particles but I'm not actually measuring the mass of the apo(a), and therefore I can get very easily fooled because you may remember one of the things I said at the outset was apo(a) has these Kringles, these Kringle folds, and it has two of the five the

plasminogen does, but one of them has 10 subtypes, and within that, there are two that can change dramatically. In fact, the small isoforms, so this is where it gets incredibly nuanced, so you have isoform #4-2, which is the one that's determining the short segment, which is the most pathologic of these lipoprotein(a)s, but you see the mass can fool you because you're dwarfing the measurement of Lp(a) mass by all of the other things that you have to take along with the ride because they're covalently bound, and it's for this reason that the particle count emerges as the better test. So the particle number does not use NMR, which is what's used when you measure LDL particles. Instead, it uses an electrophoretic separation. So it separates particles by electrophoresis, then uses an apoB stain to identify the Lp(a)'s.

And so for the purpose of this discussion, I would just say, when I'm talking about Lp(a), I'm generally referring to the particle number unless I say otherwise, and I certainly recommend that clinicians would exclusively rely on that.

Now, someone's going to push back on that and say, "Well, do I really need it if the Lp(a) mass is through the roof?" And the answer is no, you probably don't. So in the black and white cases, when a patient's walking around with an Lp(a) mass of 100 mg/dL, something enormous, which you don't see that often, yeah, the particle is very likely to be concordant with that, but in the gray area, it's not. And again, it's sort of the same argument I would have with "Why are we even arguing about measuring LDL-P versus LDL-C anymore?"

Chris Kresser: Right, right. Yeah, I mean, you see an LDL-C of 350, it's pretty likely that their LDL-P is going to be elevated.

Dr. Attia: That's right.

Chris Kresser: But if you see one of 220, it's not so cut and dried.

Dr. Attia: Yeah, and if you see one of 100, we can very easily be fooled.

Chris Kresser: Right, right. Absolutely. That's potentially someone with metabolic disease and low total cholesterol and high LDL-P. Okay, so we know now that there are strong associations between Lp(a) mass and cardiovascular events. I imagine there are fewer studies that have looked at Lp(a) particle number and events, but given what we just talked about in terms of the concordance, especially if the highest quintile, which is conferred the largest risk, that we would assume that those studies would have similar results.

Now, the next obvious question is, what causes high Lp(a)? Are we talking about the same causes of high LDL-P, or not necessarily? So let's talk about this.

Dr. Attia: So, let's start with the LDL-P, I can never resist an opportunity to reiterate why LDL-P can be elevated because I do think it's very important for a physician who's going to make a prescriptive decision to understand and think through these always in a stepwise fashion. So, there are really four things that will drive LDL particle to be increased. And so in no particular order other than the order in which I always work through them and walk my patients through them, the first is a cargo problem. We have too much cholesterol to be carried around. So, when cholesterol

synthesis is increased, that's one way that that happens, and when cholesterol reabsorption is high, that's another way that that happens. So, this first problem is bifurcated, sort of 1a, 1b, so we have too much cargo from a cholesterol standpoint and we have too much synthesis and/or we have too much reabsorption. Those are completely different events and they have completely treatments.

The second issue or third, I don't know how you're counting, is also a cargo issue, which is you have too many triglycerides. So too many triglycerides also means additional cargo; you need more boats to carry the cargo.

One, two and three are very easy to diagnose. We diagnose one by looking at desmosterol, which is a—it's the penultimate molecule in the synthesis of cholesterol, and when desmosterol is elevated, you know that it had to come through the synthetic pathway, and so we would target cholesterol synthesis for absorption. We look at phytosterols. We typically look at three or four different phytosterols, which again can't be made, so now you know they're actually being absorbed and that allows you to target a couple of things. The third one, which is triglycerides, that's very easy to measure, and then the fourth one is the hardest one to measure because we can't do it directly, but that's defective LDL clearance. So that, of course, in its most extreme state is what's driving a condition like familial hypercholesterolemia, but of course many people are walking around who do not have FH but they do have SNPs that confer defective LDL receptors in the liver and therefore they have defective clearance.

So if you want to lower LDL-P, you got all those things going for you, and as you can tell, many of those things have genetic components. And so where the genetic stuff shows up really commonly on LDL elevation is obviously on the LDL receptor front. We certainly see, although it's very rare, we see something called the type 3 hypercholesterolemia, where they have a familial increase in triglycerides that leads to this need for additional lipoprotein carrying capacity. Of course, we also see familial defects in the ATP-binding cassette that effluxes cholesterol.

Okay, but now to your question, the implication here by the way is there are many people who walk around with a familial elevation of LDL-P, but it's also highly responsive to modification and diet, especially around triglyceride which is probably driving the boat of the LDL-P elevation we see in metabolic syndrome and also with respect to synthesis, which can be driven by fatty acid selection in the diet. Monounsaturated fats can impact insusceptible people, though I haven't been able to figure out how yet. That's a different animal.

Chris Kresser: Let me interject briefly because we talked about this in ADAPT. This is less well documented in some of the causes that you mentioned, but from a functional medicine perspective, poor thyroid function, because thyroid hormone affects the LDL receptor, we've seen gut dysbiosis in SIBO and GI issues affect LDL particle number, infections like H. pylori and some reactivated viral infections and a few other factors that I think from an environmental perspective can also play a role, and we've seen that addressing those things without doing anything to specifically address LDL-P can actually lead to reductions of LDL particle number.

Dr. Attia: Yeah, absolutely. Thank you for mentioning that. It's always worth noting. Unless there's a "hair on fire" issue, you really don't want to start pharmacologically treating LDL-P in a

hypothyroid patient because of the exact reason you stated. And then secondly, always think about this through the lens of inflammation as well. I may have even told you this story, about three years ago, I had this crazy dental abscess and it was just one of those things, I was traveling so much I couldn't get it addressed. I basically spent a full month with this abscess going through a couple of drainages that didn't work before I finally had the tooth yanked out, and I probably check my blood every six to eight weeks just for giggles and it was unbelievable to see the spike I had in LDL-P during that period. It pretty much doubled from my baseline level to where I was, and it took about another two months to return to baseline. So clearly, there's something driven here through acute phase reactives, which we will talk about also in respect to Lp(a).

So, Lp(a) is a slightly different story. This is primarily genetically determined. It's genetically determined in a codominant fashion, so it behaves like a blood type, like an ABO blood type. The Lp(a) gene is located on chromosome 6, and if you look at a person's family tree, which I really encourage every physician to do when you're thinking through the lens of cardiovascular disease, I am often looking for signs of early cardiac mortality, and I'm trying to go as far back as I can into their family history, which of course, is not always possible if they don't have connection to their family and/or they're adopted or something like that. But what you tend to see are these sort of … they appear dominant in terms of what the genealogy looks like, you know, it's coming one parent, one parent, one parent, you can identify it, but again, it's not always that case. And so anyways, that's the highest level, that's what it's basically caused by, so I think for the purpose of simplicity, this is a genetic condition, and that again makes it actually the most common genetic condition resulting in cardiovascular risk. So when you think about the diseases, most people think about like FH or the other Fredrickson, Levy and Lees classifications, Lp(a) far dominates those. But there is something interesting going on, there are two things interesting I would say on this.

The first is that it's not entirely clear that the number of LDL particles which does appear genetically inherited entirely predicts the pathogenicity. So there are patients who walk around with very high numbers whose risk of cardiovascular disease doesn't seem as high as it should be given the number, and conversely, there are patients who walk around with a modest number. They might be at the 90th percentile or the 80th percentile relative to the population, but the disease has absolutely ravaged the family. And by ravage, I mean, we're talking about cardiovascular death in the 40s. Even on medication, they are still having events in their 50s, this type of disease. So the first thing I would say is there's something that's still missing from here which is also missing from a lot of cardiovascular medicines. We don't have a great way to assay functionality, which in this case, would be bad. But for example, on the HDL side, we still don't have even a clue how to assess the function of an HDL particle on the good front.

The second thing I would say—and I know you and I have talked about this offline is, and I've even seen a paper that's kind of old that demonstrated this—is that Lp(a) can move a little bit around and it appears to move in as an acute phase reactant. So actually, there's a paper out there, I think it's from '93, so it's kind of old but I can pull it up, that basically tracked a bunch of people with elevated Lp(a) prospectively and followed them through illness. And it was interesting when you watch their IL-1 and IL-6 and CRP bumps, you saw that the Lp(a) bumped with it, but it bumped in a temporal fashion that followed. So, the only thing I would explain is, if you see borderline Lp(a)s,

it's probably worth rechecking outside of anything SIRS-wise and by SIRS, I mean sort of systemic inflammatory response, not chronic—SIRS, S-I-R-S. So anyway, those are kind of two things that I think warrant a little bit of nuance in the thinking around this.

Chris Kresser: Yeah, I think that's really important to point out and fascinating. I sent you some case results from patients in our practice where we did initial True Health Diagnostics* panels on them and they had quite high Lp(a), and then we did nothing specifically to address that in terms of pharmacology, but we addressed their gut inflammation, gut issues, HPA axis, dysregulation, nutrient imbalance, other sources of inflammation like heavy metal toxicity, mold, biotoxin-related illness if they were dealing with that, and then when we retested their Lp(a) numbers, it may have decreased by as much as 40 percent, which from my understanding of what even the new drug options that are coming down the pipe, which we can talk about later, is a pretty significant reduction.

<***Note:** *Since the time of this recording, True Health Diagnostics has gone out of business. See* **this post** *for the latest updates. >*

Dr. Attia: Yeah, certainly it is, but I haven't seen a reduction that significant and of course the studies I'm referring to were all looking at Lp(a) mass which means—and again, remember, mass is such a crude proxy of the number of particles because it's producing the mass of everything that's carrying the Lp(a), and in fact we've also seen that LDL-P can have this acute phase component to it. So look, it's just one more of those things that humbles us and reminds us that we … we're probably still scratching the surface on our understanding of this particle.

Chris Kresser: Yeah, so I'm looking at this, I just want to look at the specific result. It was Lp(a) was 219 on the initial test and it dropped to 143, which is from very high risk to still high risk but considerable reduction there, and we haven't done anything yet that really focuses more on lipid metabolism, so interesting stuff. I definitely want to keep exploring this and I'm glad to have you here talking about it because I think there's more to the story than, well, it is not always the case, more to the story than we understand at this point.

Dr. Attia: Yeah, and of course the challenges, what do we do with limited information when the case of patient, as you said, here she is starting out at over 200 nmoL/L is through the roof, just for reference. I mean, I've only seen one patient in the 600s. I've seen three patients in the 400s. I've seen maybe six in the high 300s.

Chris Kresser: I had a 350 the other day.

Dr. Attia: Yeah, I mean, these are very high levels, and by the way, one thing we didn't talk about is that there certainly appears to be from a genealogical standpoint sort of a genetic susceptibility as well, right? So if you have someone with East Asian descent who has a number of X and you have someone who's Caucasian with European descent who has a number of X, it appeared to have different risk just based on the observed family history. Now, impossible for me to identify because I'm not dealing with large sample sizes, how much of that could be explained by normalizing all of the other variables, but this is one of those things where sometimes you have to be a little more cautious than you'd want to be and you're sometimes confronted with, even if a family history isn't as bad as I would expect for this number, I can't know what was going on in those patients,

meaning, the predecessors that may have been protective, and I still have to evaluate this patient sitting in front of me right now with this risk factor which can only be quantified based on the population data, which is actually the biggest challenge in cardiovascular medicine, I believe.

Chris Kresser: Yeah, right.

Dr. Attia: Challenge of translating population data puts the individual at risk.

Chris Kresser: So key, and I would extend that to even other areas as well, but particularly, an issue with cardiovascular disease since it's still the number one killer, as you pointed out earlier.

Okay, so one of the other things I want to talk about, and this has been true for other markers like HDL, we have these epidemiological studies correlating lipoprotein(a) mass at least and much higher risk of cardiovascular disease and correct me if I'm wrong, Peter, but my understanding is that the risk is so significant with this particular marker, it's more significant than any other single lipid marker. Is that correct?

Dr. Attia: That is correct.

Chris Kresser: Yeah, so pretty big deal and yeah—

Dr. Attia: Just to put that in perspective, I think the most recent look at it would suggest the following hierarchy, so if you're talking about all-cause risk, smoking would still be at number one, I think Lp(a) would be at number two, and then blood pressure and LDL-P or ApoB technically would be underneath that. So those would be your big four. And to put that in perspective, this might actually be where you're going with your question, I don't know. The one thing that people are generally surprised by is how small the hazard ratios are on these things. It's not like smoking with lung cancer, which has a hazard ratio, depending on the study, anywhere from nine to 14. The hazard ratios on smoking and heart disease are actually quite low, and it turns out that that's a product of having a highly, highly prevalent condition.

Chris Kresser: Right.

Dr. Attia: And because, as you know, heart disease is so common, it makes it very difficult to rely on epidemiology to provide us a pure insight into the risk because, one, you have a highly prevalent condition, and two, you have a very heterogeneous population.

Chris Kresser: There's a lot of noise.

Dr. Attia: Exactly. This is where the Mendelian randomizations become quite helpful because they do allow us to sort of take a better look and begin to... but anyway, I don't know if that was—

Chris Kresser: No, that is really interesting. It wasn't exactly where I was going, where I was going was, so we have these studies that showed that HDL is correlated with heart disease risk—we're not going to go ... that's a whole other podcast—but HDL-C versus HDL-P and even different types of HDL-P ... but then, some of the trials, looking at what happens when you use pharmacotherapy

to increase HDL didn't have the results that I think some hope for are expected now, where we are at in terms of trials looking at lowering Lp(a) and the subsequent effects on CBD risk.

Dr. Attia: You're absolutely right, by the way. The HDL story has gone from interesting to unbelievably interesting. In fact, just this morning, I was going back and forth with Tom Dayspring by email, and by the way, I should've said this at the outset. Anything I understand about this topic, I can really only credit to the people who have mentored me for the past six years in this space, and none have done so more than Tom Dayspring. That guy, I just refer to him almost exclusively as the national treasure.

Chris Kresser: Ah, yes.

Dr. Attia: It's not just his understanding of dyslipidemia, it's his ability to teach and just the generosity that he does and just sort of taking sort of wankers like me and getting a former surgeon up to speed in this stuff. But Tom, actually, talking about it, he's actually working on a series right now on HDL which is going to be unbelievable because frankly, it's something—I don't spend as much time thinking about HDL functionality anymore because I think we learned quite a bit, right? You have three epic failures in the CETP inhibitors including one just this summer with Merck. This clearly telling us the following: increasing HDL-C pharmacologically at best does nothing, at worst, is harmful. That ties a little bit into your question. So your question is, what pharmacologic strategies have existed to date? Well, to date, the only thing that's really been done, I believe it was through AIM-HIGH, was the use of Niaspan to lower Lp(a). Now to be clear, Niaspan lowers Lp(a) mass; it's not entirely clear how effective Niaspan is at lowering Lp(a) particle number.

Chris Kresser: Right.

Dr. Attia: But let's assume that it actually does lower the particle number somewhere. Now again, it's not entirely clear what the mechanism of action is. In fact, it's not even clear how Niaspan lowers apoB, though it could be through reducing triglycerides. But here's what we know, and we know this pretty clearly: Niaspan, despite lowering apoB, which it does, despite lowering Lp(a) mass, which it does, hasn't shown a survival benefit or an event reduction, and for that reason, as of about two years ago, most lipidologists have moved away from using Niaspan under virtually any condition except the patient who cannot tolerate a single statin, fenofibrate, ezetimibe, doesn't qualify for a PCSK9, can't afford it, and all those other things, so it's a really, really last line drug.

Chris Kresser: So, does that lack of response, do you think, have to do with Niaspan itself or that lowering lipoprotein(a) mass is not what we need to be focusing on in the same way that lowering LDL-C may not be the best target, we should be focusing instead on LDL-P?

Dr. Attia: Yeah. It's a great question. It's funny. Just by coincidence I was talking with a guy by the name of Ron Krauss, who I'm sure you know up at Children's Hospital at Oakland, who's another one of these luminary lipidologists, actually, I think it was on Sunday, and he's actually working on something where ... his thought is that the Niaspan failure specifically with respect to Lp(a) and maybe apB, by the way, could've been due in part of the increase in HDL cholesterol.

So think about it for a second. We know that Niaspan is driving up HDL-C. What if by driving up HDL-C you actually inhibit its cholesterol clearance capacity, its ability to delipidate? Because remember, when we look at high HDL-C and see the clear associations with benefit—which we knew that as early as 1979, right?—when we knew that the low HDL-C was four times more predictive of cardiovascular disease than high LDL-C, but remember, when we measure that, we are not measuring just the content of cholesterol and HDL-P. We're indirectly measuring cholesterol that was delipidated. But when you give somebody a CETP inhibitor, or presumably by whatever mechanism Niaspan is working, we may be cramming the "wrong cholesterol" into the particle. So that's one mechanism.

I think there's actually another mechanism, though this is way out there. I wouldn't be surprised, just based on some anecdotal stuff I've seen, if Niaspan is interfering with an enzyme in cholesterol biosynthesis. We know that it's driving down apoB, and so one of the things I wonder just based on some stuff I've seen is if it's inhibiting an enzyme called delta(24)-reductase, which is the enzyme that converts desmosterol into cholesterol, because one of the things I've noticed on patients on Niaspan is even though their cholesterol goes down, their desmosterol goes up. And desmosterol, we learned in the 1960s, believe it or not, is actually quite harmful. So, high levels of desmosterol, even in the presence of normal levels of cholesterol, is quite potent.

So, how could I put a bow on that? I would say that the trials looking at Niaspan to reduce Lp(a) are unsuccessful. My suspicion is that that's more a result of Niaspan than it is the result of failing to lower Lp(a) sufficiently or lowering the mass versus the particle number. But the real exciting question is, what do we do now? Now that we have a better understanding of the pathology, what do we do for a patient who has an elevated Lp(a)?

Chris Kresser: Yeah, so let's look at that in a couple of different ways. First of all, let's talk about, do any of the currently commonly prescribed pharmacotherapies do anything for Lp(a), and then what are the new treatments that are on the horizon for lowering Lp(a) particle number?

Dr. Attia: So let's pretend we're having this discussion 13 months ago. So let's pretend it's August or July of 2015. In a moment, it'll be clear why I'm saying that. So for the most high, high-risk patients with Lp(a), basically up until now the treatment of choice was apheresis, which sounds pretty extreme, and frankly, it is pretty extreme. At a frequency of anywhere from once a week to once a month, the patient would undergo apheresis, where the Lp(a) particles would be removed and the remainder of the serum would be returned, and that was highly effective at lowering Lp(a) and, I'm trying to think, it's been a while since I've even looked at those trials because I've never actually employed that therapy in a patient, so I don't recall even how large "n" was and how much longitudinal data we had in that approach, but nevertheless, that was your last go-to approach. But the approach for the majority of patients with elevated Lp(a) is to reduce residual risk by reducing apoB or LDL-P, so in a conventional sense, even for a physician who's completely on top of what's going on with risk, really, the only therapy available to lower LDL-P, which goes back to those four things we talked about—you inhibit synthesis, you inhibit absorption, you would reduce triglycerides, and you expand LDL receptors, which we do indirectly by statin-enhanced LDL receptors, the liver upregulates the LDL receptor—and that's where the game kind of changed a year ago.

So, a year ago, a new class of drug was introduced called PCSK9 inhibitors, and I'm sure you and I have even talked about this on another podcast at one point, but the PCSK9 inhibitors grew out of a very interesting observation from a paper that was published in the *New England Journal of Medicine* in 2006 that noted a subset of individuals that had incredibly low cholesterol. Their LDL cholesterol would typically be in the 20s or 30s and they also seemed completely protected from cardiovascular disease, and just as interestingly, they didn't succumb to neurodegenerative disease which you might worry about in people who had such low cholesterol levels.

It was discovered that these people had a nonsense mutation in a gene that coded for an enzyme called PCSK9 that did degrade LDL receptors in the liver. So by having a mutation and therefore a defective protein or enzyme, they have more LDL receptors and therefore they're more efficacious at clearing particles from circulation, and that explains the low LDL cholesterol.

In less than a decade, that went from concept to two approved drugs that are both on the market now. These two drugs were approved based on soft outcomes, not hard outcomes. The hard data will be out in March, I believe, and the hard outcome being the five-year mortality studies, but the soft outcome data were so impressive that this drug was approved, safety profile was great, all those other things. So now, these drugs called PCSK9 inhibitors are on the market, but with two very narrow indications. The first being patients with familial hypercholesterolemia and the second is for secondary prevention, not primary, secondary prevention for patients who are not able to achieve goal on statins, LDL goal. So that's going to be either people who are just maxed out or people who get rhabdo or people who have some other contraindication, so totally narrow.

Why do I bring all this up? I bring all this up because it turns out that this PCSK9 inhibitor also lowers LDL-P by, I mean, it depends on the patient, the preliminary report I've seen suggests it's doing so by 30 to 40 percent. I've actually seen patients have a 70 percent reduction in Lp(a) particle number.

Chris Kresser: Wow.

Dr. Attia: And so—and there's probably two mechanisms and Peter Toth wrote a very interesting piece on this earlier this year which was, this kind of was unexpected, so on the surface, you wouldn't really think that an enzyme that basically just upregulates LDL receptors would have anything to do with Lp(a) because we already know that the Lp(a), because we already know that the Lp(a) particle isn't cleared very effectively by the LDL receptor because of the interference of the apo(a) on it, but this would seem to call that into question.

In fact, in my most recent discussion with Tom Dayspring about this, he suggested that there were two things going on. One is there is some increase clearance through the LDL receptor, but that also that there's this formation of a giant immune complex which is basically constituted from the injected PCSK9 antibody itself, and the Lp(a) that contains the PCSK9 and then this entire immune complex is cleared through probably the RES system.

Again, it's another example of "I don't think we know exactly going on," but at the very least the PCSK9 inhibitor seems to lowering Lp(a) by a third and maybe more. Certainly, it is not approved for that indication and so the only patients that are taking it for that reason are doing it off-label

and paying heavily because, as you probably know and as the listener would know, that's a really expensive drug at this point in time.

Chris Kresser: Peter, what are the side effects, adverse AE profile, look like for PSK9 and have PCSK9 inhibitors?

Dr. Attia: So, pretty mild. The side effect profile is comparable to what you see with ezetimibe, which is even a more benign side effect profile than you see with a statin. And of course, when we talk about the side effect profile of the statin, that term in and of itself becomes a bit confusing because you're contrasting all generations of statin, so it's hard to compare simvastatin to Livalo; those basically are completely different drugs. But basically, patients are tolerating PCSK9 inhibitors very well. I think the reluctance that we have around them at the moment, and I might include myself in that situation, although I do have three patients on PCSK9 inhibitors for various reasons at the moment, is that it'd be great to see some outcome data. I'll feel a lot better this time next year when we have hard outcome data, and I don't know that I recommend it for somebody for whom there's an alternative at the moment.

And in my complicated patients, what I really describe is a long-term strategy. When you have a young patient, someone who's in their 30s, who has a very elevated Lp(a) and for whom the family history certainly suggests this a high priority, I prescribe to them basically a three-pronged strategy. The first thing we want to do is reduce LDL-P, so that's the conventional approach, and we're going to do that through all the tricks we know how to do, and that will also involve statins in this case because we're going to upregulate the LDL receptor as well to inhibit synthesis, but we do that within the confines of obviously not overdoing it. Then we talk about a year or two years from now, we should have enough hard outcome data that for the patient who can afford that, the PCSK9 inhibitor becomes a pretty nice bridge, and we talk about doing that in some non-conventional ways. For example, T2 drugs Praluent and Repatha have different dosing schedules. There's one that dosed once a month versus twice a month, and probably in a year or two we might actually have some primary prevention data on a lower dose of one of these drugs.

So, I see basically going from a pure LDL-P–lowering strategy to potentially a PCSK9 inhibitor strategy, but the holy grail here, you see, are these antisense drugs because this is going right after the problem. I'll explain a little bit about how apo(a) is made and then that will make sense. So you have this Lp(a) gene, I mentioned chromosome 6, and it gets transcribed into apo(a) mRNA, and then that gets translated into apo(a), and all this is going on in the liver. So the hepatocyte is the only cell in the body that can make apo(a), and you'll recall based on the subtypes within the Kringle 4, the size of that apo(a) actually determines its ability to get out of the liver or not, and once it gets out of the liver, it covalently binds to the LDL-P any way you go. Well, this new class of drugs for which the phase 2 trial was just published last fall, it's an antisense oligonucleotide, so it's a single-stranded DNA-like structure, and what it does is it binds to that apo(a) mRNA and it degrades it, so it's basically going right after this thing at the jugular. So once the Lp(a) gene codes its apo(a) mRNA, the antisense comes along and disrupts it and just completely prevents translation. So, case closed, problem solved.

Chris Kresser: Since that apo(a) may have some relationship to blood clotting, is there any concern about the effects of these drugs and our ability to form clots, or is it just in this modern environment with all of the challenges that we have and we didn't have from an evolutionary perspective that we could stand to lose quite a bit of that without concern?

Dr. Attia: Yeah, I mean, I think because you still have plasminogen, remember, this is only disrupting apo(a), it's not disrupting plasminogen, and that's still responsible for the bulk of clotting, so I think the ... I don't know if the reverse is true. So, apo(a) will increase clotting because of its homology of plasminogen, but I don't know if eliminating apo(a) reduces it. In fact, in people who have unmeasurable levels of apo(a), which is hopefully most of us, I don't think we see an increase in bleeding.

So, the only challenge going on right now ... so this drug completed its phase 1 and phase 2, the phase 2 was published, I believe, in October. I was speaking to a great lipidologist in New York, Jamie Underberg, who again is one of the guys I always turn to on the toughest cases, and he mentioned to me that they're actually still having trouble enrolling the phase 3 because of the criteria that the FDA are putting on the studies, so without getting into the boring nuances of it, it's going to take longer to enroll in that antisense trial than I had hoped, and so I was sort of hoping that this would be a drug that would be around in two years. It might be closer to four or five years, but nevertheless, at some point in time, I expect it will have phase 3 data, and my hope is that that's really the future of treating patients with Lp(a) is, let's not mess around with their lipids at all. Let's actually give them a drug that disrupts their ability to make apo(a), and all of a sudden, that phenotype vanishes.

Chris Kresser: That's really interesting. Okay. So we've covered a lot of ground in terms of Lp(a). I want to move on to a couple other things that could be hour- or two-hour-long discussions in their own right, but I know it's something you've written about and have thought a lot about, which is, so far we've been talking mostly about lipid risk factors, but what about other ways of quantifying cardiovascular risk, like calcium scoring or CIMT? What role do these play in the way that you work up patients?

Dr. Attia: Well, I think there's a rule for all of these tests, and I guess the way I approach a patient is the first thing I want to know is, old school as it sounds, I really want to understand their family history. And that's hard, as you know, because there's always other things that interfere, when their father had an MI in his late 50s but he happened to be a smoker, how much can I attribute to a genetic risk that's coming along versus a purely lifestyle-driven risk, and those are two things, but it really does begin with a really thorough family history, and I want to know everything. I want to know if grandma had high cholesterol, if she had high blood pressure, or AFib or was she a smoker, you want to know all of that stuff. Extract everything that is knowable about everybody they're linked to.

The cornerstone of my risk assessment always comes down to the phenotype, which means the blood work tells me more than anything I want to know. And so, I've been actually kicking around this idea, and at some point, I'd love to actually bring it to maturity, which is basically a 2x2. I want to be able to come up with a 2x2 that really explains this effectively, and I've had a lot of

discussions about this with both Ron Krauss and Tom Dayspring. They like the idea, so the 2x2 on the X axis would have all things that we know that are causal, yes or no, so you rank them, as in the right would be causal and the left would be not causal, and on the Y axis, you have treatable, yes or no, so in the upper you'd say yes, so you can see that breaks into a box, so the upper right of that box is causal markers that we can treat; on the bottom left, by extension, you would have non-causal markers that we also do not treat directly, if that makes sense, and then you have all areas in between. And so in my mind, I'm going through this box all the time. So, obviously, LDL-P or apoB are in the upper right quadrant because we can measure them, they are causal and they are treatable, they are targets of therapy directly. Lp(a)-P currently is for most people sitting on the bottom right, meaning, it's absolutely causal, it's not really treatable yet, although it's migrating up with PCSK9 inhibitors and eventually antisense. Oxidized LDL, we can measure that but we don't really have a drug that goes directly after it, so we treat it indirectly. That would be in the bottom right. If you go over to the top left, you have something like homocysteine and fibrinogen, which are actually treatable but they act indirectly. So for example, homocysteine does a number of things, but to me one of the most damaging things homocysteine does is it inhibits the clearance of something called ADMA and SDMA, which I know you're familiar with, but maybe for the listener, so ADMA and SDMA are asymmetric and symmetric dimethylarginine, which are arginine byproducts, and they inhibit nitric oxide synthase. And so the more ADMA and SDMA you have, the less nitric oxide you have, which is obviously problematic in the endothelium, and in addition to renal insufficiency, driving up the concentration of these homocysteine doses as well. And then in the bottom left, you have a whole bunch of non-causal, non-treatable markers like CRP or SDMA, and SDMA directly, or even HDL-C or Lp-PLA2, and then of course you have a whole bunch of genetic things in there like 9NP21 or APOE4, which are a handful of genes that people have thought about looking at here.

So, then the question becomes, how do you layer on non-blood tests? So, first point I'd make is between family history and everything I just talked about, which is a little 2x2 matrix. I'm pretty sure that I know how to stratify risk and that another test isn't going to give me a new piece of information in most patients' cases, but in most cases it does.

So let's talk about the two you brought up, which I believe you talked about calcium scoring and CIMT. Okay, so what's the calcium score? So, the calcium score, of course, it's not anatomic study, so it's not like a CT angiogram or an angiogram. It's more of a functional study. It's showing you the presence of calcification in the coronary tree. I'll tell you where I find calcium scoring helpful. I find it especially helpful in young patients in whom we don't want to treat them. We're looking for an excuse not to treat them. So you've got a 30-year-old who's got really bad numbers. You can't figure out and your intuition says, "Well ..." and certainly the mainstream approach would be, "Do nothing and revisit this in a decade." Or they don't want to be treated and you want to treat them. The calcium score there is helpful because nobody should have a positive calcium score in their 30s and 40s. So in that sense, I look at the positive telling me there's really likely to be something wrong but I always explain to the patient in great detail that negative does not tell me you're out of the woods because the plaque that kills you is not calcified plaque, so this study has not given me any insight into the different stages. And I've written a blog post on the pathogenesis of cardiovascular disease, which, if anyone's interested, would be a good place to go because I

walked through the seven histologic stages of atherosclerosis, the point being, the first three are almost uniformly patient in people by their fourth decade of life, so to suggest because a calcium score is negative you don't have atherosclerosis is, of course, nonsensical. So that's the one place that's helpful. The only thing to keep in mind is I don't find calcium scoring helpful at all in older people because frankly, we know that as calcium advances on therapy, it's probably demonstrating plaque stability. So in many ways—I should say in some ways—there are people who are actually talking about using calcium score and to follow therapy to see a progression of calcium score. I think Peter Libby actually wrote a paper about this two or three years ago which showed that you took patients that were on therapy, those in whom calcium score advanced had better outcomes than those who didn't, suggesting again the stabilization. There's another paper about two years ago that looked at calcium density on calcium scoring and stratified by density, so the lower the density of the calcium, the higher the risk. Again, suggesting the stabilizing role of calcium.

Chris Kresser: I think we also talked about this a while back, that it cannot be used serially because in some cases when the overall picture is improving, the calcium score will actually get worse, at least for a little bit of time.

Dr. Attia: Yes. In many ways, you can view a calcium score sort of an Lp-PLA2, a test that probably in a snapshot gives you a subset of risk and in a not particularly sensitive and not particularly specific way, and so for that reason, I just don't find it to be that helpful, which is not to say I don't use it. I certainly do from time to time, but I also think it's very dangerous to use calcium scoring as the centerpiece of a risk stratification program.

CIMT is effectively similar through my risk lens. It's a very different test. It's obviously looking at the intimal thickness of the carotid artery. It can be done with less radiation, though calling a spade a spade, I think these days with fast enough CT scans, the radiation on a calcium score is trivial, so that shouldn't really be the deterrent.

The other issue with CIMT is it's so user dependent, user being the technician who's doing the test, so one of the things I'm always pretty adamant about is if I'm going to send the patient for a CIMT, which I will intermittently, and by the way, I will do this in my highest risk Lp(a) patients who I'm also going to make sure they get an echo MRI for aortic stenosis. I should've mentioned that earlier. When you're working up a patient with Lp(a), it's really best practice to rule out aortic stenosis because you want to catch that before it's clinically apparent.

So, you don't want to wait until somebody has heart failure to do something about the aortic stenosis. You want to catch them when there's a gradient, but there is no evidence of heart failure. So, going back to the CIMT, it really doesn't correlate that well with cardiovascular events. Secondly, it has a lot of the same caveats. CIMT that shows intimal thickening might accelerate your appetite for treatment, but it doesn't really decrease my appetite for treatment when it's negative. You know, CT angiogram, if done at a really, really top-notch place, offers a little bit more insight because in addition to giving you all of the calcium information and all of the anatomic information, if it's done really well, you can actually get an insight into soft plaque, and so the interesting case is the person who's walking around with a highly elevated LDL-P and/or Lp(a) whose CT angiogram has widely patent arteries, virtually no calcification, and no evidence of soft

plaque. That's a bit of a therapeutic dilemma because we know that there's another component to this disease, which is the inflammatory component, which we have really lousy tools for measuring, and so you certainly look at that in a patient and you think, well, yeah, you got a whole bunch of lipoproteins, but for whatever reason they're either not getting retained, not getting oxidized, or not kicking off the inflammatory cascade that's wreaking havoc. Do I really want to subject you to the pharmacologic risks of lowering this when I don't really have evidence it's causing disease? And those are the things that kind of keep you up at night because there isn't any answer for that.

Chris Kresser: Okay, the million-dollar question that I and so many of my colleagues, and I'm sure you still wonder about is, we take the—not hypothetical patients, these are actual patients that I see all the time—who switches from a maybe Standard American Diet or maybe a higher-carb, healthy diet, lower-fat kind of 1980 and 1990 healthy diet, and let's say they're overweight, they have insulin leptin resistance, high blood pressure, a number of other risk factors for heart disease. They switch to a Paleo-type of diet or higher-fat, lower-carb diet, they lose weight, they normalize their BMI, they normalize their insulin leptin sensitivity. Their metabolic numbers all improve, their blood pressure drops into the normal range but their LDL-P goes up. What do we make of the overall quantification of risk in that particular patient? Even though we know that LDL-P is at the very top like you said, of the risk factors for heart disease, do we switch this patient back to a diet that made everything else worse in order to address that single marker?

Dr. Attia: Yeah, okay. That's … okay, I don't know the answer to that question but I certainly encounter it, but at not a terribly frequent rate. The first thing I would say is I want to make sure that I'm not missing something that's transient … I'm sorry, not acting on something that's transient. So I think that researchers have certainly written about this where, and I think Eric has written about this furthermost where … and I don't know if it's published or not, so I'm sort of confused if it's published or unpublished data, where he sort of can see this transient rise, and he's only looking at LDL-C but of course often when LDL-C goes up, if the cholesterol content's going up, there are two ways that you can sort of see that happen. One is the particles are getting bigger and they have more cholesterol, which actually doesn't seem to pose much of an increasing cardiovascular risk or actually you're just having more particles. So, the first question I have is, is any part of this may be related to a transient adjustment and adiposity? So if the patient is undergoing higher amounts of lipolysis and presumably higher amounts of fat oxidation, is that resulting in this transient change? And everything else moving in the right direction, maybe I'm willing to watch this a little bit longer.

The second thing to keep in mind is, what is the cost of doing nothing versus the cost of doing something? So this is where I think the sterol panel can become kind of helpful. So the sterol panel, which I rely on a lot to not just make therapeutic decisions but to try to understand physiologically what's going on. Presumably, you have a "pre" and "post" set of labs on this patient. You can go back and look and so—and I know you and I have talked about these particular cases before but I always go back and look at them—so you'll see a patient who sort of shows up looking with a normal LDL-P at the 20th or 40th percentile and relatively normal sterol markers, but then they go on a ketogenic diet, which is supposed to be the extreme manifestation of this, and not only do you see the LDL-P go up, but you see the desmosterol go up significantly and you see an

enormous change in typically one or two of the phytosterols, and I don't have an answer for this, but the hypothesis that Tom and I have started kicking around is that in a subset of people, the increase in saturated fat is actually driving an increase in cholesterol synthesis, and in the most extreme cases, where we've tested the hypothesis, which is making no adjustment in their fat content, which is adjusting the type of fat, I know patients on the ketogenic diet, if they're willing to eat a very monogamous diet, but you reduce the saturated fat intake significantly to, say, 25 grams per day which is actually—that's a challenging reduction for someone in a ketogenic diet—and then you increase the monounsaturated fat and you keep the polyunsaturates where they were, in the few cases where I've done that, it has always reversed the problem, which I'm staggered by because they're still consuming 75 percent of their calories from fat, which again is the most extreme case. It's just now they're mainly lining up avocadoes, olive oil, and macadamia nuts instead of all the dairy or high-saturated-fat products that they were consuming. Now, Dom D'Agostino has also noted this. He thinks it might be more a function of dairy than the saturated fat. I haven't figured out a way, on a patient-by-patient basis, that "n" is just too small to see that, so that's a first approach.

Chris Kresser: In my experience, any indicator, it's not dairy because I have a lot of people who are Paleo … I have a lot of Paleo patients who don't eat dairy and follow a straight Paleo diet and they still experience this effect. Our approach, though, is very similar because I typically will recommend, and this is what I recommended in the ADAPT course is, as the listeners know, is what I call a Mediterranean Paleo diet, which is essentially what you just described. They don't necessarily change the fat intake, but they switch more from saturated to monounsaturated fat, and I do advise less added fat, so don't put a half-stick of butter on your sweet potato, just focus on fat as it naturally occurs in foods.

Dr. Attia: For reasons I don't understand, there are some people that seem incredibly capable of tolerating saturated fat in virtually limitless amounts, provided that you've taken all the carbohydrate out of their diet, so I think high carbohydrate or high sugar, specifically, and high saturated fat is probably a deadly combo in any human. I think even John Yudkin's data from the early '70s suggested that, but in these other extreme cases it might not. So let's assume you're going to go through all those machinations, so you do the SFA, MUFA swabs, we're not dealing with just a transient effect, and all of a sudden, this is a new world order. This person is now much more insulin sensitive, their trigs are down, maybe their HDL cholesterol is up, though I'm not sure that matters so much, their CRP is down, all these other things look great, but their LDL-P went from a … let's say it was 1,200 when you started, which is 50th percentile, and it's now 2,000 which is about the 95th percentile.

At that point, I basically sit down and explain to every patient my point of view on this, which is until proven otherwise I still believe that the answer is we should lower your LDL-P. Now, it doesn't mean that in 10 years we won't have any evidence to suggest that in this setting that patient is protected from the prediction of that number due to all of the other metabolic indicators, which is by the way entirely possible, and that's certainly not an unreasonable idea. But I just want them to understand that they're taking a risk by doing that, and if they want to and we want to continue doing all these other forms of monitoring, like doing a CIMT every couple of years to try to look for

any appreciable increase in soft plaque or things like that, so be it. So basically, it then becomes a patient decision. At some point, they'll just say, "You know what? I don't want to worry about it anymore and there's such an easy and obvious cocktail of drugs that I can take here with virtually no side effect that would make it be better, so let's do it." Alternatively, they may say, "I'm morally opposed to doing that," or they may say "Well, let's try it," and if they have side effects, then they say it's not worth the risk because, of course, there's risk associated with therapy. It's probably not the answer each wanted to hear because it's a little more nuanced, but that's effectively what it comes down to.

Chris Kresser: Absolutely. I mean, we're all adults here and the answer "I don't know" or "It's not entirely clear" or "We still have a lot to learn," that is not a comfortable answer and to be honest, the thing that probably keeps me up at night in terms of this whole cardiovascular topic, prevention and treatment, is what we don't know about people who are otherwise very healthy and have no other significant risk factors for cardiovascular disease, whether we're talking about family history of blood pressure or smoking or even Lp(a), but have an LDL-P that puts them in the 80th or 90th percentile. I don't feel like we have a lot of data on risks for that particular individual. I mean, we know that mechanistically from what we understand from the process of how heart disease develops that if you take that person and compare them to a person that's identical in every other way except that they have a low LDL-P, that it stands to reason that the first person would be at higher risk, but how much higher and how does that compare with any potential risk from the treatments that we would prescribe to that person? That to me is like the big question that still needs to be answered.

Dr. Attia: Yeah, and I little get turned off by—just sort of the—I don't know what community to call them, but there's definitely a group of folks out there who is somehow under the impression that as long as you're on a low-carb diet, nothing can happen to you. You could probably jump out of a building and actually gravity turns out not to actually impact you.

Chris Kresser: Especially if you're ketogenic.

Dr. Attia: That's right, that's right. I find it a little irresponsible, especially when I see physicians, and unfortunately, I do see a bunch of these guys on Twitter, who seem to think like it's a badge of honor how high they can get their cholesterol on a ketogenic diet. I hope they're right, but I wouldn't bet on it. I also think there's a whole group of non-physicians out there who have incredibly strong opinions about it and I think it's sort of my pet peeve.

Look, when it comes to you, you're a blogger and you want to tell me what you think is right for you, that's great, knock yourself out, but the moment you become a provider and the moment you actually have to make a decision based on a patient sitting in front of you, I don't really care what anybody's saying on Twitter anymore. I don't really care what a low-carb community or ketogenic community or any community, for that matter, thinks about this issue. All of a sudden, the stakes are a little bit higher, so will we know the answer to this question in 10 years? I hope so, but until we do, I basically treat this patient like I treat any other patient, but perhaps with a little bit more patience as a lead-in to my therapeutic strategy.

Chirs Kresser: Yeah, I completely agree with you. I've written in the past about cholesterol skeptics on the one end of the spectrum, and I think it turns out that skepticism about the role of cholesterol inside of lipoprotein was warranted. And then on the other end of the spectrum are the cholesterol deniers, which is, people who deny that not only cholesterol but lipoproteins play any role in the pathogenesis of heart disease, and I think that's a very difficult argument to substantiate at this point in time.

Dr. Attia: Yeah, I've sort of stopped engaging with that crowd, not that I would ever really want to engage on any crowd anymore, but ...

Chris Kresser: Kind of like arguing with vegans, right?

Dr. Attia: Yeah, I'm not arguing with anybody. I'm an old guy now. I don't care. Everyone's entitled to their opinions. They're not entitled to their set of facts.

Chris Kresser: Yeah, exactly. Well, Peter, thank you so much for your time. This has been extremely enlightening, and I love just learning about what the latest research study on this stuff is and what's coming on the horizon because I think as clinicians in functional medicine, yes, we need to focus on the underlying cause of these problems whenever possible. In some cases, if the underlying cause is genetically mediated, there's not a pharmacotherapy or any other kind of treatment that emerges that can address these markers and lower the risk of the number one killer, it's something that we need to be paying attention to if taking care of our patients is our imperative, which I hope it is, in all of our cases. So thanks for doing what you do, Peter, and perhaps we'll get you back in the future for a much more in-depth module on lipidology. It would be a pleasure.

Dr. Attia: Sure. And lastly, if folks are interested in double-checking on any of these topics, I can't recommend Tom Dayspring's work enough. He puts up a number of things, all free content, on a site called LecturePad.org, I believe. I think you have to sign in or something like that, but it is basically a treasure trove of cases, lectures, synopses. If you're interested in this topic, that's got to be on your top five reading list.

Chris Kresser: It's amazing, and I've seen several of those lectures and even just following him on Twitter is worthwhile. He is constantly posting great links to studies with his commentary, and I've learned a lot just by following his Twitter feed. So, thank you again, Peter.

Dr. Attia: Sure, my pleasure.

Chris Kresser: All right, take care.

Dr. Attia: Great to see you. Bye.