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TRANSCRIPT - GR 09 23 22 ***"Lipoprotein(a) in atherosclerotic cardiovascular diseases and aortic stenosis"*** – Benoit Arsenault, PhD from the Department de Medecine, Faculte de Medecine Universite Laval

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UVA Internal Medicine

00:40:39Okay, Good. Welcome. Everyone.

- 00:40:42Welcome to medicine grand rounds, Thanks to all of those who have joined on Zoom and those here in person. Thanks for coming. J. I'm. Excited to introduce Dr. Benoit Arsenal. Please forgive all my French attempts to pronounce French words. Today Dr. Arsenal obtained his Phd. In Physiology, endocrinology from the University of Laval in Quebec City in two thousand and nine.
- 00:41:07He subsequently completed two Post-doctoral Fellowships, one of the Academic Medical Center in Amsterdam in the Netherlands and another at the Montreal Heart Institute, he was appointed to assistant Professor in the Department of Medicine at the University of Laval in two thousand and thirteen, and is a research scientist in Cardiol, in the Cardiology Department at the Quebec Heart and Long Institute in Canada.
- 00:41:29So his his team of researchers seek to identify, characterize, and understand how individual and environmental risk factors interact in the development of cardio metabolic diseases. His work is funded by the Canadian Institute of Health Research and the Icq Foundation
- 00:41:47Ah! Back in April he was appointed to as Co-president of the Quebec Society of lipid Lipidology, nutrition, and Metabolism, whose mission is to promote training, education, and research. In these fields
- 00:42:01he received the two thousand and eighteen, Jean de Vignon, young Researcher award from the Cardio Metabolic health. Ah, diabetes and Obesity Research method.
- 00:42:12I invited him to speak today about lifeboat protein a and its role in cardiovascular health. Please give a warm welcome to Dr. Benoit Arsenal.

Benoit Arsenault

00:42:25Well, thank you very much for that for that kind introduction. I'm pleased to be with you today to talk about my research and the field of Lpa in general. So for the next

- 00:42:42forty-five or fifty minutes or so I'll be. Ah, I'll be talking about. Ah, this very intriguing Ah, life of routine! That's all like a protein literally, and the work that we do in this in this area. So But before I go any further, can you all see my side in here? Be fine?
- 00:42:59Yeah, We yes, terrific. I'm working on just getting a few extra people out of the waiting room here
- 00:43:06great. So while this disclosure information that I have, and the funding of my research lab that you can see here.
- 00:43:17Um! And then just a quick word about the learning objectives for ah, for today's activity. Um! I pointed out three, but there'll be many more. First, I I I hope, at the end of the meeting you can understand what my protein A or Lba is,

- 00:43:37I think, for the next. Ah, i'll! I'll refer to like a protein level a as Lpa for the remaining of this presentation as second, you'll be able to determine the consequences of exposure to elevated Lpa levels on Ascbb. But also on aortic stenosis and understand the impact of Rna interference therapy on Lga levels.
- 00:44:01So if you
- 00:44:06have to go away during the talk. Uh, pretty much uh everything that I will say today is included in the uh, latest European society consensus statement on Lba that we just put out uh during the last Esc meeting, which was in the Barcelona. So uh, So this is a very interesting Well, uh, I believe guidelines
- 00:44:34that tells you uh all about Lp. A. And for the next minutes i'll just go over some of the key points that we wanted to raise with this uh consensus statement, and also, uh, tell you a little bit about what we do in my lab in the Lpa field.
- 00:44:52So ah, just ah, so that everyone is ah on the same page about Ah, the circulating lipoproteins of the human blood. And there's many sub fractions. Ah! All of them basically are ah characterized, or ah, or name add ah, a function of their particle, diameter, and density. You have Tylo microns, which are very high after a meal,
- 00:45:21and they are enriched in triglycerides. And also there's a very low density lipoproteins. These are also triglycerides, which, like proteins that are secreted by Ah, deliver there's in the human blood a very small concentration of intermediate density, lipoproteins, and ah! The most of the cholesterol in the human blood is actually transported by low density, like proteins. Or Ah Ldl.
- 00:45:50Ah! Today my talk is going to focus about another. Ah sub fraction of Ldl. Which golf, which is called Lpa. Ah, it's very similar to an Ldl particle in terms of ah diameter and density, and it also Ah, ah transport Ah, apple protein b one hundred. So
- 00:46:12there's one apple nipoprotein b one hundred per ldl particle, and there's also one. Ah April protein deep per lpa particle.
- 00:46:24Ah, so one important thing that Ah, I I think you us people need to realize when they get a standard limit. Profile is that you cannot estimate Ah Lpa level based on a standard like a protein. Ah, profile you actually have to measure. Ah Lpa, because actually in in patients that have ah that have that don't have, or a very low amount of
- 00:46:52the the Ldl Cholesterol or the cholesterol that's transported by Ldl. Is actually transported almost entirely by low density like proteins, Whereas, if you're looking at the a person with higher Lp levels. And we're estimating that about fifteen to twenty percent of the world population has an Lp level that puts them at a much higher risk of a broad range of cardiovascular diseases.
- 00:47:20Um! Well, you someone might think that the cholesterol could actually be transported by the Ldl. But since, as I just told you, the Lba has the same density and the same diameter as an Ldl, so you clearly overestimate the amount of Ldl
- 00:47:39that you that you measure, and you underestimate the amount of cholesterol that's actually transported by Lda. So one really needs to assess the Lda level; first, to to know, to determine if the patient is at high risk, but also second, to to get a good estimation of what the Ldl Cholesterol actually is.
- 00:48:01So this is what an lba particle. Ah looks like it's as I told you recently. It's very similar to an ldl particle, or as you have. Ah, the phospholipid membrane! Ah! Inside of it is Ah Cholesterol Esters as well as strikely right. There's Fossil Liby is a free cholesterol on the membrane. There's an April like over the one hundred per particle of Ah,
- 00:48:31now the the the most important difference between lba particles and an Ldl. Particle is the addition of this Apollo protein here. That's called aable life of protein. Literally.
- 00:48:45So it's a very complex protein. Actually, it's subdivided into different
- 00:48:54tringle uh for uh! Repeats uh, and there's also many domains in in that in that Lp: So there's uh the kingle at like the kingle for type. Two here that you see can be very uh heterogeneous from one

person to another, and that will, as we'll see in the next slide that will ultimately determine the the levels of Lpa. Now, on the Kringle four type nine. You see, there's a system in residue

- 00:49:24that will actually form a dice off it bridge with Ah, another Cysteine residue on unable B. So it will bound non-covalently to ah to the able B part,
- 00:49:38and on the cringle for type ten is actually a strong Lly scene by being site, which is a site where ah oxidized fossil, it can actually be added to ah to Lda So one of the reasons that actually that Lba is so hydrogenic is that it actually carries the the it's. The main carrier of oxidized fossil lipids in the in the human blood. So ah! Part of those
- 00:50:05dangerous effect of Lp. Are actually due to not necessarily to be a A or the a moiety of Uh Lpa, but actually to that, to its phosphollympic and one analogy that I I really like to use when I compare Lpa to Ldl. Is this one, so you can refer to Ldl as a baseball, so sure uh you can uh baseball can actually be very uh, very
- 00:50:35dangerous if you Ah, if you get hit by a baseball on the forehead or something. But ultimately, if your kids will tell you that they want to go play baseball in the backyard, you'll let them play
- 00:51:05heavy medieval flail in their backyard, so on a perparticle basis, the Lpa will be much more atrogenic and much more damage to the vascular and Italian than Ldl.
- 00:51:22So. Ah! Why does the April, like protein little A isoform size matter? Well, the reason is that it matters because it will ultimately determine the levels of lipoprotein literally the plasma levels of like a protein as a way. So in some individuals
- 00:51:41well across individual actually Lpa can vary up to a thousand folds, and the blood levels of lipoprotein literally are almost entirely explained by genetic variation at the chromosome six which, where the lpag is expressed, and
- 00:52:01the best part of the genetic variation in Lba is explained by the number of Tringle, four type, two repeats that one can have
- 00:52:11individuals can have. Ah, only four repeats of this isoform here. They can have eight. They can have twenty, four. They can have up to forty, and you see the a boy that has forty cringle for type two. Ah, isoform is much bigger. Ah! And it's actually associated with lower levels of Lpa. So the higher the size of the Iso form of the Tringle.
- 00:52:39The lower the Lpa level is, and the smaller the size of a boy is the higher the particle concentrations are. And the reason for that is quite simple is that it takes to the cell a lot of energy to actually produce this, Lpa.
- 00:52:58And it. It will take a long time to mature in the Golgi apparatus, and it'll take a lot of time to get secreted. So a small a boy particles gets agreed very rapidly, whereas particles that have a higher isoform size gets degraded to a much slower rate,
- 00:53:20and it doesn't really matter If you have a small or a large a-way isopore size, you get the same amount of oxidized fossil lipid because they don't bind to the tringle for type. Two they bind to the Tringle. Ah, four times ten repeat of Lda. But, on the other hand, if you have a small Iso form, you have a much higher number of circulating Lb. Particles. Therefore you have a higher concentration
- 00:53:49overall of oxalized, phospholipid, and ultimately that that is what will matter to cardiovascular health.
- 00:53:58So a quick word about the regulation of Lpa biosynthesis and its catabolism. Ah! It's still not entirely clear how the ah lp particle is formed. According to some ah studies, a boy is actually secreted in the bloodstream, and it can bind to an Ldl. Ah. Article
- 00:54:22in the blood. There's also some evidence of of interaction between a Pope with April A and A. B directly in the cytoplasm of hepatocytes that will ultimately lead to a secretion of Lpa. So that's still hotly debated in the in the literature right now, and also it's even more debated. I believe it's the clearance of a lth. There's a

- 00:54:50several lines of evidence that suggests that the Plasmidogen receptor can actually bind April A. Because April, it has a high resemblance to glass. Minigen.
- 00:55:01It can be ah feared by a hdl receptor scavenger receptor B one receptor. But I think there's good evidence suggesting that the low density lipoprotein receptor the ldlr
- 00:55:18it could actually be an important receptor theory. Lba. Particles from the blood because of its high affinity, not to a
- 00:55:30and when the Ldl receptor gets binds to an Lp. Particle in the cell. It can get recycled. It gets degraded, and the cell can use the cholesterol content.
- 00:55:46So ah! Before I go any further. I I think it would be ah interesting for the audience to ah understand how I I became interested in ah in Lba. So um! We've known that Lpa. Exists for several decades. In fact, it was discovered in one thousand nine hundred and sixty three, by a Swedish researcher named Carrie Berg, and in the nineteen seventy S. The one thousand nine hundred and eighty S.
- 00:56:14And the one thousand nine hundred and Ninetys. There have been several studies linking Lpa levels to the risk of getting heart attacks or strokes.
- 00:56:27But as these studies were published, there were a lot of also negative studies, showing no association whatsoever between lda particles and
- 00:56:38the risk of cardiovascular diseases; and part of the reason why there has been such so many negative studies in the is that our assets are our biological assets to measure out the particle or measure algebraic concentration.
- 00:56:54We're really suboptim. So they were really poor in actually telling us. Ah, the actual concentration, or the number of Lt. Particles in the blood, as ah as many of them actually found to be. Ah frigal for type two repeats so in in some individuals with a higher Ah, a a smaller iso From size there was really an underestimation of the number of a of parts, so as Ah, the field of
- 00:57:23epidemiology became more active. We've seen a lot of genetic studies actually resurrecting the Ld Particles as an important risk factor for cardiovascular disease,
- 00:57:40and that was about at the time when, uh, I was a a full doctoral fellow, asking myself uh what I was going to study if I if I had the chance to one day open up my own lab. So uh, and it really was. I wasn't really looking for. I had heard about it because I was uh involved in in research during my Phd studies. But when I did my also my first call, so I can answer them. I work with the T. And study, which is a treating
- 00:58:10new target study. Ah! Which was, I think, I was the first or the second study to show that higher doses of the higher doses of Statins actually had more ah incremental benefits in terms of cardiovascular prevention, and we had ah measured eighteen biomarkers in ah in that study. Ah! And to identify biomarkers of residual risk, and we identified only Lba as the as the most ah important. Ah,
- 00:58:38victor of residual. Where's risk in these individuals?
- 00:58:43Then I move on to another project where you
- 00:58:46and we did. We participated to the Gist consortium. The just consortium is the genetic investigation into statin therapy, where we actually try to identify genetic predictors of Ldl. Response to statins and
- 00:59:01and to make a long story so short there, Aren't, that many genetic variants that have a big effect on the Ldl response. And actually the biggest
- 00:59:12uh genetic risk Factors influencing. Ldl: response was actually Lba, because well, we know that status uh reduce Ldl. But in the setting of a high Lpa levels since that insult, that influence Lp. Cholesterol, they have a a lower effect on Ldl Cholesterol, because these, as they actually measure Ldl and Lp: So that was another interesting point from that.
- 00:59:40And then from Amsterdam I I moved to Montreal, where I studied the genetic of calculation and aortic about calcification and aortic synosis,
- 00:59:51and a colleague of mine actually was in Montreal as well. Ah, George China! So this published the first that she was a genome-wide association studies. For Ah! They were develop calcification and

identified Lp. As the top tunic locust, and we a year later we replicated that. Ah, that's finding in a couple of large school. So it was really I. I was not really looking for Lba, but they see that every ah

- 01:00:20project I was involved in identified Lpa as an important determinant of the of the of the thing I was uh investigate. So it didn't take much more for me to start a lab on Lpa. And actually, yeah, that so. So another reason why I did. I did study Lpa. Is that actually the top? The top genetic risk factor associated with
- 01:00:47with your exenosis is a common variant in Lpa. It's called Rs. One hundred and four, five, five, eight, seven, two, and it's the most important genetic sniff in the Ldl. It's associated with Lba levels and astrosterotic cardiovascular disease
- 01:01:05that eight percent of the population has. Ah, a one or two, G, all of desktop. And when I look up. My! Ah! When I downloaded my own data from my twenty-two and B reports, it turns out I was actually a carrier of Lpa out of this snip and I have an lpa of ah two hundred animals per later, which puts me about in the ninety percent percentile of the of the population distribution. So
- 01:01:34it really got me interested in the in the Lpa field.
- 01:01:39So this is actually a uh one of the genetic studies that that really was eye-opening for the community, and it was actually one of the first uh Mandela randomization study that was published on Lp. They're actually in two thousand and nine. There were three studies. This is one of them. The brocard is like what they did in that study is this was very simple. They uh recruited three thousand patients with a heart disease and three thousand controls.
- 01:02:08They measured their lp level. They measured several genetic variants within the lp locus, and they found that people that had zero at Lpa, raising Allele at a very small concentration of Lba.
- 01:02:25Now, if you had one ah variant in Lba, you had a higher level of Lpa, close to about sixty milligrams per destiny, or that was associated with an all in the risk of ah of heart disease; whereas in people who are very unlucky, and we're actually carrying two, and Lda raising variants. All their Lpa level was much higher. It was about one hundred milligrams per this leader, and their risk was,
- 01:02:53and multi multiplied by five. And so you really see here, at those response effect of not only Lpa, but Lp. Rising. Ah, alleles on the risk of ah hard business! So simply by looking at the the variance you can see. Ah, the effects! So we don't really need to know the Lpa concentration. Ah! And at that time the assets were also getting a little bit better. So. Ah, so now! Ah! Since two thousand
- 01:03:23and nine, two thousand and ten, we really see a resurrection of the of the interest of this scientific community for Lp.
- 01:03:34So we know that Lpa is associated with myocardial infarction with cardiovascular disease.
- 01:03:42Ah, but there's several lines of evidence that show that Ah Lpa is also probably the most important or the strongest risk factor for ah calcificiortic bio-inosis. It's also a shit associated with heart failure with ischemic stroke with peripheral arterial disease with cardiovascular mortality and also all cause mortality. So ah! So to maybe to compare this with with Ldl concentration, we see an epidemiologics,
- 01:04:12studies some association between Ldl and
- 01:04:16coronary artery disease, but we don't necessarily see association with Ldl and Cbs, and also mortality. The association is not really strong, but Lba is, is really associated, and actually quite strongly to uh, all of these uh, all of these outcomes. And uh, we're starting to see a lot of studies showing that Lba would actually be uh even one of the top uh genetic rest
- 01:04:46factor for all cause mortality. So it can actually be a longevity. G. The.
- 01:04:55To explore this. Ah further. We published a paper a couple of years ago. Ah! Assessing the effect in a genetic study on parental lifestyle in a cohort that's called the Uk while we. So this is a a very big cohort of
- 01:05:14five hundred thousand participants from the United kingdom, and they had. So So the the

- 01:05:26they made available uh the genome-wide Association results for uh, for or actually the one to design it for all these participants, so that the scientific community can actually ask questions about uh, all sorts of things. So we're actually interested in healthy lifespan in them. But since this was actually a cohort of adults uh it. It takes a long time before
- 01:05:56to actually die in these cohorts, but they answered a bunch of questionnaire, and we had actually access to the age at which their parents passed away. So we separated the cohort into people that have a high parental lifespan or not one hundred and fifty,
- 01:06:16and we investigated the effect of Lpa rising snips on the odds of having high parental lifespan. And ah! It turns out that there was actually quite a strong effect of ah about. If I remember correctly, we did a a genetic score of about twenty steps in the Lba field in the Lpa. Ah, Gene, and we found that patients that carried the most Lp. Rising. Snip had a shorter parental lifestyle.
- 01:06:44It didn't really matter how we define lifestyle, whether it was the top ten percentile, the top percentile or higher paternal lifespan or higher maternal lifespan the effect of of Lpa on shorter parental lifespan was quite significant.
- 01:07:00Uh, in the same uh paper we investigated the effect of uh, the blood levels of Lpa in uh, in the epic Norfolk study. So the epic Norfolk study is also a study from the Uk It was started actually in one thousand nine hundred and ninety-three. So we have more than twenty year Follow up on these individuals, and you see a very high All cost mortality event rates here. Uh
- 01:07:29in in this study and in that investigation we actually look at the different percentiles of of Lpa. And we found that patients that were in the top fifty percent, also five percent of the population, and actually a much higher, all cost mortality, risk. Ah! So the difference between ah, this ah five percentile of the population and patients who are in the bottom. Fiftieth percentile was actually nine percent or close to nine percent.
- 01:07:58And And remember, this is, we're actually looking at all cause mortality here. So we're looking at body count, basically and a nine percent difference in absolute risk, I believe, is quite important. Ah, it's important to say here that we're looking at a cardiovascular mortality. Ah, the difference between the top and the lowest group is also nine percent. So Ah, Lba is, is really a strongly associated with all costs,
- 01:08:28but because it is so strongly associated with cardiovascular mortality. So there's no effect really of Lp. On uh other uh phenotypes that are outside the cardiovascular system, but because their effect on cardiovascular is so important that it really explains a significant percentage of the differences in in our cost mortality in the general population.
- 01:08:56So all of the data that I've shown you recently was either in participants from the Uk or from Denmark. And
- 01:09:10the data is actually quite clear that Lpa is also associated with four cardiovascular outcomes in different ethnicities.
- 01:09:21So in uh, uh. So Lp: levels is actually highest in in black individuals. Uh and uh, it's probably explained by uh, the difference in a a a isoform size. So for a given size of Lp. I support Blacks seem to have higher Lp. Now, that being said for the same increment in Lba, the uh
- 01:09:49risk of Ascbd is really proportional to the effect of these increments in Lpa. Whether it is in black individuals and Hispanics in white
- 01:10:04East Asians, and as well as in in Southeast Asia. So we really
- 01:10:11need to do more research and different ethnic groups, maybe to identify the specific population thresholds that will put one at high risk of as Cvd um. But the data is actually pretty clear that Lb. Predicts four outcomes in in ah in everyone regardless of their Ah,
- 01:10:35so let me switch gear a little and explain. Ah, the basic pathogenic mechanisms of of of Lpa, I think. Ah, we have tier evidence, so suggesting that the oxidized fossil depends on Lba is ah is actually quite ah, quite important, because it really has, and I believe, really pro-inflammatory effects, whereas if the oxidized possible,

- 01:11:05a really drive endopelial cell dysfunction, and this will really activate macrophages within the arterial wall, They'll secrete many cytokines, many apoptosis markers, and it will really activate. But macrophages and
- 01:11:24and also promotes muscle, cell proliferation and migration So they really have, because of their pro-inflammatory effect they have pro-ateral cerotic effects, but also broadcasts and funny effects.
- 01:11:39So this is, for instance,
- 01:11:41uh a study from uh my colleagues in in Amsterdam, where they uh they actually perform uh, eighteen Fsdp. And individuals with high or low wellpa, and these are individual from the general population. And you can see that uh, you really see? Uh, you're starting to see some, some early signs of information in the carotid, and in the aort of patients with the with healthy, that Don't necessarily have
- 01:12:11a heart disease. So this is evidence suggesting that the Lba could actually be involved in the early steps of
- 01:12:23So this gave me the idea to uh to actually do the same thing. But uh, not necessarily. Look at the carotid or uh the uh aorta, but really look, start looking directly in the uh aortic cloud. So we set up in our uh center this technique uh of uh of that Ct: but with another tracer. So instead of using the oxy glucose that's uh associate with uh information we use uh
- 01:12:51uh eighteen F. Sodium chloride, which will really bind to the uh, uh, to the hydroxy appetite. Uh, that's being built in inside the uh aortic cloud. So so it will really be a a specific marker of phone formation basically in in the uh, in in, in that, in that specific study we look at the effect on the
- 01:13:20and these are individuals once again from the general population. We have thirty patients about in in each group, and we see a clear effect of having high Lba on
- 01:13:35on aortic valve a micro calcification assessed by this by this tracer. So it
- 01:13:44another line of evidence suggesting that Lpa. Is associated really in the early steps of not only atrocities, but also aortic stenosis.
- 01:13:55Now I'm going to go through this slide rapidly. This is another study that we did, because we really wanted to investigate whether or not Lba is associated with the Arctic stenosis,
- 01:14:11and but regardless of its impact on coronary artery. This is because, uh, actually so sometimes. Uh well, as many of you know the pathological mechanisms meeting, or the arteries are sometimes the same, or very similar to calculation or externosis. So we really wanted to investigate in in genetic association uh studies where the predictive value of Lp. Was the same in patients with cad
- 01:14:40versus without curry, artery disease. And we find ah, very clear evidence suggesting that even in patients without binary artery disease, Lba will ah will be associated with ah with aortic stenosis. So it's really a specific effect
- 01:14:57 on both disease rather than uh a mere consequence of having a see. This is important, because there's really at the moment there's no treatment. There's no medical treatment aside uh replacing the val that will uh actually influence the course of the disease of calculation, or think about the noses. So uh so There's a lot of research going on right now uh in this in this area
- 01:15:26uh to uh, really try to find the mechanism that that through which uh lba uh cause uh calciviki, or dixonosis, and also astrolosis. So uh over the last couple of years uh or over the last five or six years we've been very active in that
- 01:15:45in that in that field.
- 01:15:48Uh, we've shown here uh that uh, the blood levels of Lpa will uh, directly, especially in individuals that have it to endothelial dysfunction. They'll be able to penetrate within the uh the artery wall. They'll drive uh macrophage from cell formation. They'll cause uh inflammation uh through the generation of
- 01:16:17auto tags. And so here an Lba doesn't stand for like a protein little a. It stands for Lys ofosphatic acid

- 01:16:26apologies for the confusion here. But, uh, Lp. Is a type of oxidized fossil that that will really uh drive the osteogenic uh differentiation of the of Uh. They, or think about the interstitial cells, and will ultimately, uh cause calcification within the your.
- 01:16:49So this was the summary figure from a paper that we had published in circulation already seven years ago, showing that through its effect on the receptor on the lysopostatic acid,
- 01:17:03a receptor in the valuer interstitial cells, the uh the licop for specific asset that's cleared by all the tax and out of action is actually transported by Lp. In the human blood. It will really write the calculation process through the activation of the Nf. Kaba B. Um Ah, transcription factor, and it will increase the production of aisle six,
- 01:17:31but also up. Ah, another Ah, but important driver of ah calcium vacation, which is bone morphogenic protein, too, so and that will ultimately drive down the process of mineralization, and in osteogenic and transition.
- 01:17:48So ah! So we know that ah statins are actually the cornerst of ah cardiovascular prevention and treatment. But ah! As has been shown in many randomized clinical trials of outstanding
- 01:18:06the uh residual risk associated with that and therapy is actually quite high up to uh seventy percent, because uh, in in most cases, in those studies uh statins actually reduce uh, the risk of cardiovascular outcomes by twenty to to to forty. So there's an important residual uh cardiovascular risk, and we have good evidence suggesting that not only because of the T. Andp. Study that I'm sure. But
- 01:18:34from other studies, from other genetic association studies, that Lba is really an important driver of as Cvd. Risk in patients that are actually already receiving Ldl Cholesterol,
- 01:18:50and this is uh the results of a genome-wide association study for uh for residual cardiovascular risk. So this was conducted in patience already with coronary artery. This is looking at the effect of various on having a second or third uh heart attack, and here we see so on on that uh block. Each dog actually represents a single with you. By volume or business
- 01:19:20we can see that the only genome white, significant sniffs are on chromosome six in the
- 01:19:29in the Lpa region.
- 01:19:32These investigator performance and metaphys is showing that in patients that already have
- 01:19:39uh uh heart disease, Lpa is actually associated with, uh, the risk of having a second uh heart attack, and that's also been shown in another Meta analysis, published in a lancet four years ago. Uh in uh seven studies that had uh
- 01:19:58in seven I actually stand in trial, so even in patients that were treated with stadiums Ah, having an Lba Ah! Above seventy-five milligrams per designator was associated with the risk of ah cardiovascular diseases.
- 01:20:15So for the next? Uh. So for the next few minutes I'll i'll briefly talk about? Uh, how do we lower uh Lpa levels? And how do we treat actually patients with? With? Uh with high Lp: Because, uh, there are several little bit lowering broad uh on the market. Uh, and and most of them uh actually provide either no reduction or a very small reduction. That's probably not clinically significant, because you really need to have
- 01:20:45large reductions in in Lba to ultimately influence the course of azeroserotic, cardiovascular disease.
- 01:20:54But I am going to talk for the next few minutes about anti-sense. I'll go to cleared
- 01:21:01so basically
- 01:21:04Asos work by Ah, by inhibiting Ah, the translation of Rna into protein So the central dogma and molecular biology goals is following. So Dna makes Rna and makes proteins.
- 01:21:18We really see,
- 01:21:20not only with the Covid vaccine, but, uh, with it within the field of of Astro. Strong and cardiovascular disease will see a lot. Uh I I actually believe that we'll see a lot of these Rna interference therapy, and making it to the clinic uh, probably sooner than we Then we think so.

- 01:21:39So actually there's several ah there are several ah different mechanisms, through which ah anti-sense, oligopolyodes can influence ah gene expression. So basically Ah, there is a an anti-sense All the go to the under development for ah lva develop a jointly by a company called Ionis and the artist.
- 01:22:07So basically the antisense Aldehyde technology will actually reach the cytoplasm of the cell. It will penetrate inside the nucleus where it will bind to the Mrna of interest by Franklin Watson. So basically when the Lba gene
- 01:22:35produce the mrna of Lpa can actually be inhibited by an anti-sense strand that's targeted against this Mrna.
- 01:22:46It can be degraded within the nucleus by
- 01:22:50by some Rnas. And what's really interesting about this molecule is that the second-generation, antisense, oligonucleotide are actually
- 01:23:04ah made with. Ah! Ah! A galaxy and the galaxy moiety is actually a sugar that will bind to a receptor that's only expressed by hepatocy. So we have a drug that's very selective, and that we know that that will only be effective in delivery and not in ah in other organs
- 01:23:30so currently. Ah! In the field of livid lowering therapy. Ah, there's some ah anti-sens all the nucleotide, but also some si Rnas, which operate by a similar mechanism that actually prevent. Ah! Broke the secretion of ah proteins that will cause disease.
- 01:23:50And these proteins, Of course I talked extensively about the Api, but there's also uh are an interference therapies that are under investigation against other at genes That influence uh Ldl cholesterol, but also triedless right risk, like a protein metabolism, such as A, B, C, three, e, n gpl, three, and the and Pcs. Nine. So uh, between now, and the end of this decade we'll have a lot of cardiovascular
- 01:24:20studies testing the impact of these different
- 01:24:24technology on the effect of and their effect on lipid levels, but also on cardiovascular outcomes.
- 01:24:32And there's been uh, So as I mentioned earlier. Uh, there's one uh drug that's uh further than the others in in terms of development, and that that drug is called Ella Carson. Uh, it's been uh tested already in a phase two randomized critical trials in two hundred and eighty-six patients with uh established Cd.
- 01:24:57And you can see here, uh, the injections are happening either every four week or every two weeks. Uh, and we see very important reduction. So for the those that's uh that's been used at twenty milligrams every week we see an eighty percent reduction in Lba, and in that we see that ninety-eight percent of the of the patients uh actually had at the end of the study
- 01:25:27a plasma level that was below fifty milligrams per year, which is pretty much a threshold at which we see an increment in Cvd Risk happening,
- 01:25:42and the safety profile of pellet. Carson is actually
- 01:25:47ah, ah! Pretty good for the for the moment there is obviously the most important side effects are injection. Ah! Leading to injection, site, reactions. Ah! That that are
- 01:26:03more common than in placebo, and that are, and that seems to be, those dependent. But
- 01:26:13what you should know is that these are actually most of them are mild, and they don't last very long in time. So we see a very acceptable drop out rate in in studies like that.
- 01:26:31And ah! Of course that's very interesting to know that. Ah Lpa can be reduced by this. Ah! By this agent. Ah! But at the end of the day. What we want to know is whether a Lp reduction will actually translate into ah
- 01:26:48better cardiovascular outcomes from for patients, and
- 01:26:53the horizon trial is actually currently testing that hypothesis.
- 01:27:00So
- 01:27:01in this trial there's about eight or nine thousand patients with established cardiovascular disease that are

- 01:27:11that have been recruited. The enrollment, as terminated a couple of months ago, and these patients are being randomized to this drug. Tq, two hundred and three zero, which is also called Ella Carson, uh eighty milligrams once monthly
- 01:27:31or Matching Placebo, and the treatment period will last about four ah, four years, and with the minimum follow up time of two point five years, so we'll have to be patients. We'll have to be patient. We hope that the results will be available in Ah, two thousand and twenty-five.
- 01:27:54So But before the publication of this of this trial
- 01:28:02is every actually most of the limit lowering guidelines I actually suggest to still measure Lba. But the question is, what do we do in patients that have? Ilpa? If we have nothing,
- 01:28:20reduces a lp level,
- 01:28:22there's actually a lot of things that that we can do. Uh. So this is a a graph from our scientific statement, looking at the effect of Uh lb plasma concentration here, and according to baseline risk of Ascbd events. So what we see here is that in patients that have a very low phase,
- 01:28:48Lp. Is associated with the higher risk of as cvd in in virtually any category. So um so a patient that has that has a a low baseline risk, but a high Lba level could have a risk that's equivalent to someone that has a higher Ascbd risk, but with low wellp level, and that might actually influence, if we consider an Lba in treatment algorithms that
- 01:29:17that we should actually,
- 01:29:19uh be probably more aggressive in terms of uh, of managing other lifestyle or uh or other clinical risk factors such as Ldl Cholesterol blood pressure, and Google. So uh, we really believe that the treatment uh should be uh given according to the overall absolute risk of as Cbd.
- 01:29:48And that Lpa can really influence the course of Lba. So
- 01:29:54in patients that have, for instance, ah, a very low risk and a low lba, we wouldn't really necessarily recommend preventing therapies, but even in patients with a low risk, and we should probably consider a drug intervention that that will target Ldl: blood pressure and glucose, and
- 01:30:16and in patients that have a very high Lp: So one hundred milligrams per desk later or two hundred nanopols per liter um, Then ah! Depending on what your asset provides, Then ah! In patients that have, and this is probably the nineteenth or ninety-five percent out of the population that we should really be more ah, more aggressive. Ah, with Ah, with the preventive! Ah,
- 01:30:44uh! So. Uh, we're starting to hear a little bit more about uh Lpa in the in the late press, and this is a sorry uh Bob Harper. Some of you might know him because he's a fitness influencer in the in the United States, and a couple of years ago he uh underwent a cardiac arrest, and was uh unconscious for a for several hours. He's really
- 01:31:14he really is, Mr. Fitness in the United States, but he still had a heart attack. Uh, and he and it turns out that he had a very high Uh Lpa level. So this is an example showing that it really can uh uh
- 01:31:29influence anybody regardless of their baseline risk factor profile The
- 01:31:35So uh, in summary uh, I I just want to put out here the uh graphical abstract of the consensus that we had published to really uh highlight the recommendation from the European at the Sterosis Society uh consensus statement that Lpa should be measured at least once
- 01:31:54in adults that the interpretation of Lba concentration should be done in the context of absolute global Cvd risks,
- 01:32:04and that ah risk factor intensification or our management by lifestyle and medication should be ah done in the context of absolute global Cdd risk, and that we ah eagerly await the results of specific, healthy, lowering therapies that will ah be available in ah three years from now.
- 01:32:27So with that I'd like to thank you very much for your attention, and I'll be happy to take questions.

01:32:35Great. Thank you. We'll give you a look around for pause.

- 01:32:42So, Ben, I'm going to get um a microphone in the center of the room here that people are going to ask some questions into. Then I'll monitor the chat here. If anything comes through

Benoit Arsenault

01:32:51great,

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01:33:08can you see me on your screen now.

Benoit Arsenault

01:33:10Yes, I can see you

UVA Internal Medicine

01:33:13So I think One of the first questions I had was: It was interesting. You mentioned the Osteo. I guess Genesis effect of lipoprotein a, and you mentioned bone, morphogenic protein,

- 01:33:28So that made me think of some other disease states, particularly like polymer hypertension. Um are there as your lab, looking at any other um organ effects of lipoprotein a outside of, like the cardiovascular system in particular, and trying to maybe connect the dots between that all cause mortality and perhaps um disease states and the kidneys and the lungs in other organs.

Benoit Arsenault

01:33:53Ah, yeah, that's a that's actually a very good question, and I we have a pretty good ah department. Ah, a research! Ah! A group here in the pulmonary hypertension, and maybe I should reach out to them to see if they, if they have lb measurements in in these patients. But this is a very rare condition. Um. So Ah! And Lba is very frequent. Ah, I Lp. Is very frequent so

- 01:34:20and maybe it can actually influence the vasculature in these individuals. That's actually a very good, very good hypothesis. So thanks for bringing it out,
- 01:34:31and with regards to other organs. Ah, I think the kidney is also important, because we see that exposure to high Lpa levels is actually associated with a higher risk of kidney disease. Now, the risk is not as high as what you would see with as Cbd. But it's there's still an effect, and there's also an effect of renal disease on raising Lba because of ah of the massive,
- 01:35:00the amount of protein that will be. Uh, that's probably influenced either uh Lpa. Uh that that probably into with both Lba production, but also uh reduces the metabolism of of Lp. Cause some of the Lp. Can actually be clear also, not only by the liver, but by the kidney as well. So, uh so maybe It would be interesting to investigate if we know from the Uh Lbl. Or in trial
- 01:35:30that that that Lba lowering is beneficial. Maybe it would be interesting to investigate this in patients with kidney disease.

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01:35:39Quick, one,

- 01:35:41I think you can see the chat. Is that right?
- 01:35:44Because you're a co-host? There's also a few questions might pop up there.

Benoit Arsenault

01:35:48So basically ah, the question is, what is the contribution of lifestyle factors diet and exercise to Lpa levels and or size? And that's actually a very good question. And I wrote a review article on this a few a few years ago.

- 01:36:06Basically, if you look at genetic studies, and one of the one of the most
- 01:36:14well, I would say one of the best Ah! Genetic studies was from ah Iceland actually where they performed Ah! Whole genome sequencing in patients, that I also had Lb. Measurements, and they clearly showed that you know the genetic contribution to Lp. A level was one
- 01:36:31close to one hundred percent. Basically. So um.
- 01:36:35And but on the other hand, there's been many, many studies that have looked at different types of diets or physical activity. We even look in our lab at bariatric surgery, the effect of bariatric surgery on Lpa, and we see some effects. Ah! So! And depending on the on the diet, or the intervention.
- 01:37:01Some of them increase lpa, some of them lower. Lpa. I think bariatric surgery lower. They'll be a little bit at the beginning, because it also really lowers Ldl a lot, and the Lp. Level kind of went back up after a year. So I think
- 01:37:18one should not base their diet on its effect on Lda, because the data is really all over the place.
- 01:37:29On the other hand, uh, we also need to have a intervention, trial, or dietary intervention trial in patient specifically with high Lpa, because most of these studies have been performing the general population. Maybe just, you know, measured Lba because they have that available. And so it really doesn't matter if you have like a super low wellpa. And even if you increase it by fifty percent, it will still remain

Unknown Speaker

01:37:59very low.

Benoit Arsenault

01:38:00So we're going to. We need to do um a specific dietary trial or our lifestyle intervention trials specifically in patients with high up. But, uh I I wouldn't try to get this funded, because, uh, you know, it's really almost entirely jet that being set. And when we've shown this in the that the risk associated with the Lba is really altered by

- 01:38:30having adequate a lifestyle
- 01:38:36Ah! Risk factors so in in patients that have you know that are Ah, that follow the dietary guidelines, or on a healthy plant-based diet, or are are physically active. They don't smoke, they don't drink too much alcohol. They have adequacy, et cetera. And then we see that the absolute risk really lowers. So. Ah so Lba can actually be less ten or the risk associated with Lpa

- 01:39:05is is maybe not as important as it is in patients who have, for instance, for metabolic health. So even though you know, having healthy lifestyle factors doesn't necessarily decrease lpa, it decreases your absolute risk of ah of heart disease and um, and that's ultimately what matters at the end of the day.
- 01:39:32So I see another question here. Uh, I think I'll read it out loud. So. So the question is, I've heard Mike Brown refer to the residual cardiovascular risk after Ldl. Loring as being attributable to time, meaning, if we lower Ldl for the whole lifestyle. Then the risk would go away. You suggest that we refer to it as gram years of Ldl. Do you think a similar mechanism operates for Lpa. And if so,
- 01:40:00how might it impact the future? A future trial based on Uh, I gotta say, I completely agree with this. So uh the grand Year's concept is very similar to the back year's concept. When we refer to cigarette smoking. So, for instance,
- 01:40:16smoking one back a day is not as important if you started smoking last year, compared to if you would have started when you were sixteen years old, for instance.
- 01:40:28And the same is true for Ldl. I completely agree with this, and for Lpa. My guess is that it's probably the same thing as well. Now we don't have the trial data to support this.
- 01:40:40But the genetic beta is so. It is so robust that I I really think we can envision the same thing for Lpa. Because Lpa, like uh Ldl, is, is causative in the chain of
- 01:41:00metroslerosis leading to atrosterotic cardiovascular disease. So the
- 01:41:06the longer and the higher your exposure to Lpa is the higher the risk is, and we see ah, a linear association in genetic physiological studies with Lpa and the risk of as Cdd. So we have every reason to believe that it will be the same as this grand year's. Uh.
- 01:41:30But we, you know we're we're gonna need to have some trial data to back this up,

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01:41:36and we have another question here in the audience.

- 01:41:39A few more in the chat coming up, one of the things that stood out to me was the effect of with the lowering medications on lip or protein. Aoles, especially at statins didn't seem to have much of an effect. So if I start screening for high protein ailer levels in my patients,
- 01:41:57should I be more aggressive about escalating them to like is Atmi or Pcsk nine inhibitors.

Benoit Arsenault

01:42:03Uh: yeah, I think uh, ultimately uh, what really matters here is that uh you? If you have a patience with a patient with high Lpa, then, uh, and for instance, like a family history of heart attacks due to a Ilpa. Then uh I'd say, yeah, go for it That, you know. Drive down the Ldl. Uh as low as you can, as early as you can, so that will decrease the absolute risk of,

- 01:42:32and it might uh decrease uh lpa associated risk. It will not decrease your Lt. Or maybe a little bit with Pcsk. Nine. But even in Dcsd nine studies we see
- 01:42:43that while there's a couple of controversial studies, but I I mean there's really convincing evidence showing that the benefits, even in patients with Ilpa is driven by the Ldl reduction, maybe a little bit by the Lb. A reduction.
- 01:42:57But it seems to be trivial, so, so my suggestion would be yet to tackle all the risk factors that that you can't control blood pressure and control glucose levels and most importantly, lifestyle ads.

Unknown Speaker

01:43:16Okay,

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01:43:17I think that it looks like That's the question is from the audience, and I don't see any other ones coming through the chat here.

- 01:43:24But I thought that was a great conversation. It was a good amount of basic science, translational science, and some steps for the future.
- 01:43:31So we really enjoy you. You come spending time with us today, and I hope you have a good rest of your day. I'm sure you can't see my face at any of this. I've kind of been like a little bit of a ghost. But hopefully this I've been too disorienting.

Benoit Arsenault

01:43:44No worries. Thank you so much, Sam, and thank you. It was really fun. Thanks for the questions, and I hope you learned a thing or two about Ltd. And I hope you'll start measuring it.

Unknown Speaker

01:43:56Yes, very good.

UVA Internal Medicine

01:43:58Thank you. Bye.