Part 2 – Lp(a) Discovery Neurology Perspectives Transcripts

Introduction (00:06):

Welcome to the American Heart Association's Heart 360 Podcast. This podcast brings together diverse groups of clinical experts from around the world to share their expertise, insights, and models on how to implement guideline directed medical therapy to combat the number one cause of death cardiovascular disease. Each episode contains focused professional conversations for providers across the spectrum of care, targeted at improving patient outcomes through quality improvement. And now today's episode,

David Peña (00:39):

Welcome back to the Lp(a) Discovery podcast. This is part two of our two-part series *Perspectives from Neurology and Cardiology*. I'm David Peña, program consultant and host of this podcast series. Through the Lp(a) Discovery initiative, we aim to explore system level practice patterns for patients undergoing testing for elevated Lp(a), as well as develop national models for standardized testing. Today we are pleased to have two distinguished doctors from the Duke University Health system, both a cardiologist and a neurologist to discuss their clinical perspectives on Lp(a) testing. We'd like to welcome back Dr. S Shah and Dr. El Husseini. How are you all doing today?

Dr. Shah (01:25):

We're doing well. It's great to be back. I'm still excited from our last discussion and looking forward to discussing more. I think that this is such an exciting topic and that there's so much that's going to be coming in the future that it really will redefine our approach to cardiovascular prevention.

David Peña (01:50):

Absolutely. So I'd like for us to talk more about what the future holds for treatment in the Lp(a) space and talk more about cascade screening, which we talked on a little bit. So what can cardiologists and neurologists expect for treating a patient who has Lp(a) moving forward?

Dr. Shah (02:14):

Yeah, no, I think this is a great question. I'm happy to take the first stab at it. So I think it's really important to understand that with the current therapies that are in clinical trials for lipoprotein(a). We've seen a lot of promise in the phase two clinical trials with very high absolute reductions in lipoprotein(a) and of course pretty good safety profiles and that's really important. Of course, we don't have outcomes, so as much as we all in the community hope that there's going to be an improvement in major adverse cardiovascular events, we need to stay tuned and wait to really be sure once the results come out that that is truly the case. So a lot of anticipation for sure, but if in the best case scenario there is an improvement in major cardiovascular events, there is an outcomes improvement, then it really opens up our toolbox for therapies.

(03:19):

For the highest risk patients who have elevated Lp(a), that can reduce Lp(a) anywhere between 85 to 95%. That's pretty remarkable and I think you're going to start seeing patients with more precise targeted or biomarker targeted approaches to prevention. So let's say for instance you have a patient that has extremely high LDL but also high Lp(a). We have the tools, established tools that can lower LDL with good outcomes, but then that patient may also benefit from an additional treatment for Lp(a). And so you're doing a little bit more to modify risk assuming that the clinical trial data shows benefit, which

is an important assumption. And so you definitely have that. Those are siRNA based therapies. They're antisense oligonucleotide based therapies, so those are definitely in the future. You also have therapies, oral based therapies that are currently in clinical trials, one being an oral PCSK-9 inhibitor.

(04:36):

Again, we know that the monoclonal PCSK-9 inhibitor and some of the siRNA based PCSK-9 inhibitors lower Lp(a) modestly, but there's another therapy that can lower Lp(a) and then in investigation are also certain CETP inhibitors that have also been shown to lower Lp(a) at a similar modest level. So those are what I would call the novel therapies that are currently being investigated. Again, very investigational that are out there that could both indirectly and directly of course inhibit Lp(a). And so that's a really important, I think part of our future. We again have to make sure that there's actually benefit in terms of what we can do today, like we talked about in our last episode, there's some actionable items today and it really focuses around modifying what we can modify. So lowering LDL as low as you can, my personal practice has been to treat patients with elevated Lp(a) as secondary prevention patients.

(05:53):

So I like to get their LDL at least to less than 70 if they've not had an event, if they are already secondary prevention and they have high Lp(a), I try to aim even lower somewhere below 55 if I can. That's my personal practice. I do consider aspirin therapy in the primary prevention setting for patients with elevated Lp(a) if their bleeding risk is low, it's again all through shared decision making of course going through the risk and benefits, the currently available evidence, the strength of the evidence, but that's something I consider. And then I try to modify other modified risk factors if they have issues with blood pressure, for instance, weight, I really, really emphasize good lifestyle, so good diet exercise patterns that are consistent with our guidelines. And then I also mentioned cascade screening, which is something I know we'll talk about here. But essentially cascade screening for our listeners is just screening first degree relatives of a patient with elevated Lp(a), so either parents, siblings, children, and then if you identify any relative with an elevated Lp(a) as well, then screening that person's first degree relatives, so parents', siblings or kids. And just going along that line because you may identify people that are at risk who don't know that they're at risk and who may benefit from more aggressive risk factor modification because remember Lp(a) is very genetically mediated and so that's where this whole concept of cascade screening can be beneficial.

Dr. El Husseini (07:34):

You made great points in addition to this from a stroke standpoint, I think that similar to what you said, we're waiting for the big trials now that are well designed to evaluate the effect of cardiovascular outcomes with new treatments that decrease lipoprotein(a) significantly. So the future questions are going to be how many patients with ischemic stroke are going to be included in these studies? At least two of the ongoing clinical trials are including patients with ischemic stroke and including stroke as an outcome and included in the primary outcome with pre-specified analysis. So we will need to wait for these results to see if again, it is beneficial to treat lipoprotein(a) for stroke prevention. I think the future is going to hold to determine is it beneficial to treat it in all strokes or any subset of strokes. With strokes, it's similar to our other cardiovascular health.

(08:54):

There are multiple competing risks. So where does the risk of lipoprotein(a) lie and how much does it increase stroke risk when all the other risk factors are controlled? Also, I think it is hopefully the future will also shed some more light into is lipoprotein(a) contributing to racial disparities in stroke incidents? Because we do know that in the US black Americans have higher risk of stroke incidents and stroke

mortality, and we also know that individuals of African descent have higher lipoprotein(a). So how much is lipoprotein(a) contributing to these disparities? We definitely know that hypertension plays a big role in that, but understanding other that additional contribution would be very important. Like I mentioned in part one, I think from a stroke standpoint, we also know that the stroke risk increases in menopause and menopause is associated with multiple cardiovascular changes and metabolic changes.

(10:12):

And this is a time where lipoprotein(a) may increase even though it is genetically determined, but it may increase a little bit more during menopause. So are there specific populations that we need to be looking at? We also know that individuals with kidney disease and liver disease have increased stroke risk, and this is definitely through multiple mechanisms, but how much does lipoprotein(a) play a role in this and does it need to be targeted in special populations? And then also there are some studies suggesting elevated lipoprotein(a) and pediatric stroke, so understanding more that role and evaluating potentially treatments in this population is also going to be relevant.

Dr. Shah (11:10):

Yeah, those are excellent points and a lot of important questions that we still need to answer. And I think it raises awareness to the idea that lipoprotein(a), if you look at the molecule, it's a very heterogeneous molecule, the lipoprotein(a) particle, it can be very different across people. So for instance, for those that know what the molecule looks like, the size of the lipoprotein(a) can be very variable based on the number of we call cringle repeats that are on the molecule. And then also different single nucleotide polymorphisms or snips exist for different lipoprotein(a) molecules I guess if you will, at the highest level. And so essentially what that means is lipoprotein(a) may also have variability in how it behaves in an individual's body. So certain SNPs may be more prone to atherogenesis, others may be more prone to, let's say calcific aortic valve disease or calcific valve disease.

(12:22):

We're starting to see evidence of that both observationally and as well as genetic studies. And so that's another area in the future that it would be great to see answers for at least a lot of questions, but also see answers for those questions in terms of how does modifying Lp(a) influence the natural history of let's say calcific aortic valve disease. And so that'll also be another important thing in the future as well as understanding the interaction that various particle sizes of Lp(a) play on other cardiometabolic comorbidities, diabetes being another, there's interesting relationships and literature between the risk of developing diabetes and the level of Lp(a) that you have. And so all of those things, especially when we have therapies that drop Lp(a) at high absolute values, it'll be interesting to see how it modulates some of the other things that we start seeing Lp(a) be associated with.

David Peña (13:31):

Dr. Shah, we have discussed PCSK-9 inhibitor treatment. Can you please share with our listeners the role it may have in folks care with elevated Lp(a)?

Dr. Shah (13:47):

Absolutely. That is a fantastic question. Now the best data that we currently have is what in part one Dr. El Husseini had highlighted was data from the earlier PCSK-9 clinical trials looking at the effect modification in patients with, of course elevated LDL but also elevated Lp(a). And there seemed to be a benefit even in that subgroup of people with elevated Lp(a) and we know that indirectly PCSK-9

inhibitors drop Lp(a) modestly about 20 to 30%, which is something that being said, based on the totality of literature currently, and I'd love to get Nada's thoughts here as well. The role of PCSK-9 inhibitors to me is just another way of modifying LDL-C. So it's a way to make sure we get our LDL levels low because that we know is really important. Patients with elevated Lp(a) is, especially if they have high LDL levels too, because LDL is very modifiable.

(14:56):

And so I think PCSK-9 inhibitors are very important in patients both with and without elevated Lp(a) who have very high LDL levels. And there's suggestion based on the literature that lowering the LDL in those that also have high Lp(a) is even more beneficial to that patient. So using PCSK-9 as a way to get to your LDL-C goal I think is extremely important. And it's not just necessarily the PCSK-9 inhibitor and it's really how you get there in my opinion. Maybe there is some drug specific benefit in this case, potentially some effect modification with the Lp(a) lowering effect. But I think the bigger picture is getting to your LDL goal where our evidence really points us to at the moment. And so if that is with the PCSK-9 inhibitor on top of a statin, great. If that is with statin and a non-statin like ezetimibe, great. As long as you get your LDL-C down, I think that you're moving in the right direction. Nada I'd love to hear your thoughts though.

Dr. El Husseini (16:08):

I agree with this approach. I would add that we know that ezetimibe and statins are not going to decrease lipoprotein(a), and it seems like in both of the PCSK-9 trials for FOURIER and ODYSSEY that there was a higher benefit for these agents when lipoprotein(a) was high. I do think that still the initial step is to control LDL-C, but in those who don't have good control of their LDL cholesterol with a high intensity statin, I would probably have a lower threshold to get a PCSK-9 on board than adding ezetimibe just because we know it'll reduce lipoprotein(a). Now again, I'm not suggesting that this should be a standard or a guideline, just a thought process that maybe there will be benefit because again, there are no studies yet showing that that should be standard. But I just wonder because adding PCSK-9 is likely to decrease lipoprotein(a) by 30%, the big question is going to be, is decreasing it by 30% going to be enough to add a significant stroke prevention decrease? Actually that creates the stroke risk even further

Dr. Shah (17:54):

For sure. And I think a lot of it depends on what's the baseline LDL value that you're starting with because there's, in addition to some therapies indirectly dropping Lp(a) by 30%, others not touching the level at all. If you have a patient who's on max tolerated statin or cannot tolerate a statin who is at risk or let's say has atherosclerotic cardiovascular disease has elevated Lp(a). I completely agree. I mean my first approach off the bat if they're starting at an high LDL level is to go for a PCSK-9 inhibitor to give them the best benefit and drop the LDL as low as I can and hopefully confer benefit with the Lp(a) lowering. So yeah, in my practice, just like not a highlighted, I do tend to reach for the PCSK-9 inhibitors after statin therapy to really modify the LDL as low as I can or give the patient the best shot to get their LDL as low as I can. But we need certainly more data to help confirm this practice pattern. I think everything is very patient specific. So through shared decision making, coming up with the right approach for the patient is usually the best approach at the moment.

David Peña (19:21):

Absolutely. I think what we found with testing, it's genetic. And we talked previously in part one about cascade screening. So if a patient were to have an elevated Lp(a) result, who in their family would you recommend get a test?

Dr. Shah (19:43):

Yeah, so I would say if a patient has an elevated Lp(a) level, then I would recommend all first degree relatives to get an Lp(a) test. So parents, siblings or children. Now for children, I want to throw a caveat. Some people have much younger children. I usually recommend at least at adult age, like the onset of adulthood 18 or higher. But that's is just, maybe it's the parent in me that doesn't want a young kid to get stuck for a blood draw, but I do think at least at adulthood, just to know what baseline risk we're starting.

David Peña (20:33):

What about testing, considering coding barriers with insurance? I know that could cause a lot of apprehension concerning actually testing patients for Lp(a). Do you have any insights there?

Dr. Shah (20:49):

Yeah, so testing for Lp(a) has been very, in terms of cost and access has been very variable, and there's some health system specific barriers potentially. There could be patient specific barriers, provider specific barriers, lab specific variables. So a lot of different things That plays a role in how easy it can be to get a test. In my personal experience, I've never seen patients get a hard time from payers about a lipoprotein(a) test. Either they get an estimated cost and go elsewhere to a third party lab vendor to get it for cheaper or the cost isn't too prohibitive to get the test wherever they're seeing their provider. So I've not had too many barriers, but I also understand that barriers do exist. And so what I say is definitely keep an eye out in your community on what the costs are at different places to get labs. I think that's a good first step. It may be cheaper to go to a third party lab vendor for the patient than doing it at the health system for whatever reason, either because of insurance barriers, patient access barriers and things like that. But now that Lp(a) has become a little bit more widely known and the assays to test Lp(a) are more widely available, there are a lot more places to get tested.

David Peña (22:38):

This has been a really great discussion as we wind down. I really liked the way you framed that Lp(a) is actionable now. Do you have any departing words of action for any of the providers listening?

Dr. El Husseini (22:54):

I would like to just add that collaborative care in individuals who have elevated lipoprotein(a) is helpful and needed connecting back because this is a lifetime risk that they have. So connecting with a primary care physician, connecting with a cardiologist who do this work and co-managing this risk factor is going to be important. And I can speak that my collaboration with Dr. Shah on a clinical basis has been very rewarding for me and my patients. Again, we're lucky to have a Duke Cardiometabolic Prevention Clinic focused on heart to control cholesterol, individuals who have statin intolerance or who have lipoprotein(a) elevation. And so collaborating with this clinic and with Dr. Shah and his team has been, again, very useful for these patients.

Dr. Shah (24:10):

And I would say ditto. My collaboration with Dr. El Husseini has been just an amazing experience, both for myself. I learned so much from her as well as my patients who we share. And I think it adds to the concept of circling our care around the patient, keeping the patient in the center, making sure that the patient's providers are all on the same page and so that the patient keeps getting the same message, doesn't necessarily get confused. Everyone is sort of on board with the plan. And I think when the patient's providers are all on the same page, it really builds confidence for the patient in their care, and they're more likely to adhere to recommendations that are evidence-based and really help optimize their risk for the lifetime.

Dr. El Husseini (25:01):

And added to that is, of course, the shared decision making with, again, the patient at the center and being presented with all the options and the evidence that we have so far.

David Peña (25:13):

Absolutely. Well, thank you so much to Dr. Shaw and Dr. El Husseini for sharing all of your insights, care considerations and perspectives on lipoprotein(a). To learn more about Lp(a), listen to our Lp(a) Discovery podcast series or watch professional education presentations at heart.org/lpadiscovery. Thank you so much.

Closing (25:43):

Thank you for listening to today's Heart 360 episode. Today's content discussed current barriers and care and how these barriers have been addressed in the communities featured. These views do not necessarily reflect the American Heart Association. American Stroke Association's official position. The association does not endorse any product or device. For more quality improvement information and resources, visit www.heart.org/quality.