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Assessing the Effectiveness of Lp(a) Lowering Therapies in Clinical Trials

Dr. Cheeley:
You're listening to *Heart Matters* on ReachMD. I'm Dr. Mary Katherine Cheeley, and I'm speaking with my fellow ReachMD host, Dr. Alan Brown, past President of the National Lipid Association, to discuss current Lp(a) trials for important updates presented at the 2023 National Lipid Association Meeting.

Dr. Brown, thanks for joining me.

Dr. Brown:
My pleasure, Mary Katherine. Thanks for asking me.

Dr. Cheeley:
So I attended the 2023 NLA Scientific Sessions here in Atlanta, and they were excellent, but one of my favorite presentations that we had was your presentation on current Lp(a) trials. Can you give us an overview of what you talked about?

Dr. Brown:
Yeah. I really talked about two outcomes trials that are underway, which is what we've all been waiting for a lot of years. Now that we have agents that significantly lower Lp(a), there are two studies of patients with established coronary disease, one with an antisense oligonucleotide and another with a small inhibiting RNA, and these are randomized prospective trials to look at reduction in cardiovascular events.

Dr. Cheeley:
Can you do me a favor and kind of talk through the differences between the two studies specifically? Because I think you did an excellent job of talking through the two different study populations that they had in those trials.

Dr. Brown:
The first trial called the HORIZON trial is with an antisense oligonucle—nucleotide called pelacarsen, and the second study, which is using small inhibiting RNA called olpasiran, they're both studies of patients with established ASCVD.

So the HORIZON trial is a CV outcomes trial, phase 3 outcomes trial. They randomized into getting monthly doses of the antisense oligonucleotide pelacarsen, which lowers Lp(a) up to about 80 percent. There's over 8,000 participants, and they are being followed up for major cardiovascular events. To get into the study, they had to have Lp(a) levels of more than 70 milligrams per decilitres. The other study, OCEAN(a), which is a study of olpasiran, a small inhibiting RNA, this drug will lower Lp(a) up to 98 to 100 percent. It is a drug that's given every three months, so a little less frequently, and they had approximately 6,000 patients being randomized.

So both groups required that patients had prior coronary events. The study with pelacarsen, the HORIZON trial, also included people with prior strokes, and then the endpoint for the HORIZON trial with pelacarsen includes stroke plus cardiovascular events, and the

study with olpasiran, the OCEAN(a) study, is primarily looking at cardiovascular events excluding stroke as an endpoint.

Dr. Cheeley:
So let me make a comment for our pharmacists that are listening because I'm a pharmacist, and that's my heartbeat at all of these. We only have one siRNA that's currently on the market with inclisiran. We don't, to my knowledge, have any ASOs that are out there, or maybe very few. Can you kind of talk about what we should think about as clinicians, what pharmacists should be aware of, the pharmacodynamics of the drugs and how they work?

Dr. Brown:
Well, we did have mipomersen. The decision was made not to continue marketing it, but it was an effective drug.

So you're right, though, in terms of small inhibiting RNA, or siRNA. The only one on the market is inclisiran right now, and the encouraging thing is that inclisiran has been now followed from the initial dose-ranging and safety trials out past five years.

Dr. Cheeley:
Yeah. And I think it's important to know how we think about siRNAs. They certainly have a long duration of action, but their actual lifespan or their half-life of the drug in your system in the circulation is very short.

Dr. Brown:
Yeah. Well, that's an important point. The half-life of inclisiran is about nine hours, so it is out of your circulation quickly, but remember that siRNAs bind to the RISC complex inside the liver cell, and they turn on RNases that destroy the target messenger RNA. In the case of inclisiran, that would be the messenger RNA for PCSK9. But that siRNA double-stranded piece of nuclear material stays on the RISC complex for the life of the hepatocyte, so you don't find it in the circulation, but it is in the liver cell over the long-term, which is how the efficacy lasts so long.

Dr. Cheeley:
For those just joining us, you're listening to *Heart Matters* on ReachMD. I am Dr. Mary Katherine Cheeley, and I'm talking with Dr. Alan Brown about his presentation at the 2023 NLA meeting on current clinical Lp(a) trials, and we're going to shift gears a little bit and talk about the HERITAGE study.

So, Dr. Brown, jumping out of the current clinical trials that are happening and jumping into a study that was more recently published about the population of patients with an elevated Lp(a), let's talk through the HERITAGE study. What was the objective of that study?

Dr. Brown:
Well, this looked at the prevalence of Lp(a) in patients with established atherosclerosis, so the folks that they looked at had prior MI, had prior stroke, or had peripheral arterial disease, and it was actually a pretty robust epidemiologic study. There were just under a thousand sites in 48 countries, and they were looking at LDL levels and Lp(a) levels, whether they were measured, whether anyone had an Lp(a), and if so, what were the levels? And were the levels different in different demographics?

So there were about 48,000 patients that got enrolled and had their data evaluated, and of those 48,000 patients who had established events, cardiovascular events, only about 14 percent had had prior measurements of Lp(a), so it tells you from the beginning that it's not top of mind for most clinicians. The median Lp(a)s weren't too high, about 18, but what was noticed that was interesting was that Black patients had three-fold higher Lp(a) levels than Caucasians, and there were also higher levels in younger individuals than in women, so this was an interesting observation. In the past, we've seen that Blacks have had higher Lp(a) levels, and though there was initially a thought that that might not correlate with higher risk—that maybe their normal should just be higher—it turns out that's not true and that Lp(a) levels are higher in Blacks. But their risk is also higher by virtue of the elevated Lp(a). So with each passing year and each new swath of the data we learn more.

Dr. Cheeley:
Yeah. I think it's really interesting. They did the subset of the study just in the US population, and even there, those results rang true. In Black patients it was significantly higher.

How do you think that HERITAGE will impact further studies that we're doing? Now that we have this information about younger females and Black patients, in particular, what do you think that's going to do for our clinical trials moving forward?

Dr. Brown:
Well, I think like all data you have to look at it with a little bit of a jaded eye. I mean, think about who got the levels drawn. These were people who had cardiovascular events. People that we'd be particularly worried about and who might be, for example, a female with early cardiovascular events, possibly somebody with a high Lp(a), so I think there's a selection bias looking at people with events where the levels are going to be higher in certain individuals. It makes sense to me that younger individuals without a lot of other risk factors who have an event may have had it caused by Lp(a), which, as you know, occurs in 20 percent of the population.

So I thought it was very interesting. I think it will help us evaluate things. But looking at the overall population base levels of Lp(a) and then evaluating risk based on that is going to be helpful also. So I think having two therapies on the horizon that are very effective for lowering Lp(a) is going to cause many more studies and many more opportunities to better assess risk.

Dr. Cheeley:
Yeah, I totally agree. Your point about selection bias is perfect. Of course, younger patients who got selected for this trial are going to have higher Lp(a)s, but I also think that's super important for clinicians to think through. When you have a younger patient, look for a high Lp(a) because to your point also earlier, it's a family genetic predictor of risk, and so, if we can find it in a young patient who had an early disease, then we can look at their kids; we can look at their brothers and sisters; we can try to save someone else an event by intervening early with the therapies that we do have now.

Dr. Brown:
Yeah, I can't agree with you more. I think that was very well said. I think they're a group of different people that you absolutely don't want to miss Lp(a) on. One would be anybody with a family history of premature atherosclerosis, especially, if they have risk factors that aren't really explained. And another group that we don't think about that much are patients with very high LDLs who have a negative genotype for familial hypercholesterolemia. We know that people with very high Lp(a)s can masquerade as FH depending on the size of their Lp(a) particle because the Lp(a) can sometimes be falsely measured as LDL. So if you see somebody who's not responding to statin therapy, even if they don't have super high LDLs but you just don't see the drop in LDL that you expect, it's important to think about Lp(a), which might be masquerading as LDL. And of course, Lp(a) does not go down with statins, so that would be a reason why you might not see the efficacy in a statin trial that you thought you would. And it's true for familial hypercholesterolemic patients also.

Dr. Cheeley:
Yes. This has been such a great discussion. I always love spending time with you. This has been a great conversation looking at the current landscape of Lp(a) research, and I want to thank my fellow ReachMD host, Dr. Alan Brown, for joining me today.

Dr. Brown, this is always a pleasure. Thanks so much for being here.

Dr. Brown:
Thank you. The pleasure was mine. Thanks for the invitation.

Dr. Cheeley:
For ReachMD, I'm Dr. Mary Katherine Cheeley. To access this and other episodes in our series, visit ReachMD.com/HeartMatters where you can Be Part of the Knowledge. Thanks for listening.