Title: CardioNerds @AHA23: An Extended Duration Short-Interfering RNA Targeting Lp(a)
Participants: Dr Maryam Barkhordarian and Dr Steven Nissen
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Dr Maryam Barkhordarian

"Hello, everyone, and thank you for listening in on CardioNerds Radcliffe cardiology coverage of AHA 23. My name is Maryam Barkhordarian, internal medicine resident at Hackensack Meridian Health and a CardioNerds fellow. It's a pleasure to meet with Dr. Stephen Nissen, academic chief officer of hardened vascular and Thoracic institute at the Cleveland Clinic. Among the several trials, he is the primary investigator of a clinical trial on lepodisiran, a short interfering RNA targeting on lipoprotein(a). Thank you so much, Dr. Nissen, for meeting with us.

Dr Steven Nissen

It's a pleasure.

Dr Maryam Barkhordarian

Thank you. In addition to other classic risk factors such as diabetes and hypertension, lipoprotein(a) has an additional risk factor for atherosclerotic cardiovascular disease. Data showed that elevated lipoprotein(a) is associated with an increased risk of ASVD in patients. Pharmacological agents targeting lipoprotein(a) has been the subject of recent clinical trials. Dr. Nissen, do you mind giving us an overview of this trial and how it differs from other previous trials on olpasiran or other alternative medications targeting lipoprotein(a)?

Dr Steven Nissen

Yes, well, first of all, as you said, it is an important risk factor. It's important for everybody to know that we think that about 64 million Americans and 1.4 billion people on the planet have elevated levels. It's been untreatable, and we are really on the verge of a new era where we can treat this disorder.

Now, we studied a drug known as lepodisiran. Lepodisiran is a short interfering RNA. It's a little different structure from some of the others in that it has a hairpin connection between the two RNA strands. And the nucleotides have been chemically modified to resist degradation by ribonucleases. So after the strands separate in the hepatocyte, the drug is actually first delivered to the hepatocyte because it's connected to a sugar known as GalNAc. That acts as a means to getting the drug into the hepatocyte in high concentrations, it then degrades messenger RNA, which leads to a very substantial reduction in lipoprotein(a).

Now, because it's connected to this sugar, GalNAc, it has a residence time in the circulation that's very short. It's completely gone within 48 hours. So you administer it, subcutaneously, it gets into the circulation, but it doesn't stay there very long. It concentrates in the liver. What we saw in this trial is different from what has been seen previously. Levels at the top dose of 608 milligrammes, and we studied from four to 608 milligrammes. At the top dose, levels plummeted, and by day 29, they were below the lower limit of quantitation. They were unmeasurable and out to 281 days. At the top dose levels of lipoprotein(a) were unmeasurable. They were below the lower limit of quantitation. That's 9.4 months. And if you go out to 337 days or 48 weeks, which is the longest time we followed, these patients levels were still 94% reduced. Even the half-maximal dose produced very protracted reductions in lipoprotein(a). We've really never seen a short interfering RNA with this duration of reduction in lipoprotein(a). So that's what's really new here. There is a manuscript that describes many more details in JAMA that people can read that will explain a little bit more about what we did.

Dr Maryam Barkhordarian

It is interesting to note that with targeting lipoprotein(a), we can help optimise the ASCVD risk in our patients. Did you find any surprising results in this trial?

Dr Steven Nissen

Well, I think we were surprised by the duration, the intensity and the duration of effect. Now, it's important to understand that this is a small phase one trial, only 48 participants, so we have a lot to learn. Phase two is well underway. Phase three is in planning. We're going to learn a lot more. Whenever you do a phase one trial, the primary outcome of interest is safety. And like other short interfering RNAs, this drug was very safe. There really wasn't weren't any treatment, immersion, adverse effects. There was a little bit of pain at the injection site. Every injectable has that, but there really wasn't anything else. What makes short interfering RNAs so unique is that they're very targeted. They do one thing, they degrade one messenger RNA for one protein, which means that they are inherently rather safe. And I'm very encouraged that we're really entering a new era of drug development. We've moved from the small molecule era to the targeted genetic therapeutic era, and this is one of a number of developments that will lead, I think, to important advancements for patients.

Dr Maryam Barkhordarian

That's so interesting. And I assume that we are not far from this medication being used in the lipid management.

Dr Steven Nissen

Well, in this case, that will be a long term project to do the phase three trials, which are required by regulators. But there are other nucleic acid therapeutics that are in phase three. They're different. One of them is an antisense oligonucleotide known as palicarsin. That's in a fully enrolled phase three trial of 8300 patients that we're also running. And that trial will likely give an answer in 2025 or 2026. So we're within the next couple of years, we have the opportunity for the first time in history to treat elevated lipoprotein(a). It's an exciting time for those of us that have been waiting for two decades to be able to treat this abnormality.

Dr Maryam Barkhordarian

Yeah, definitely. Do you foresee its impact in the clinical practice like clinicians start using it as soon as well?

Dr Steven Nissen

We do think that this will be used in clinical practice if it is successful in reducing events, major adverse cardiovascular events in phase three. But we have a problem. The vast majority of people that have elevated lipoprotein(a) don't know they have it. We published a study of 48,000 people in almost every country in the world who already had had a cardiovascular event, and only 13% of them had had a previous LPA level obtained by their physicians. So we have an educational problem here that if we are going to be successful, we have to get people to start testing for lipoprotein A. And we think actually everyone should be tested in their youth, probably in their twenties or earlier, because once a level is obtained, it's the level you will have for your lifetime. And so if we know who has an elevated lipoprotein(a), we're going to be able to treat people and prevent disease, which of course is what we want to do.

Dr Maryam Barkhordarian

So what we know is that it's going to be an add to our lipid panel.

Dr Steven Nissen

Well, I hope it is. Places that have sophisticated prevention programmes are obtaining lipoprotein(a) on a routine basis. Unfortunately, not enough places are doing this. And so I have a message here, which the message is, let's start testing, because as these therapies become available, we've got to know who has the disorder so that we can know who to treat.

Dr Maryam Barkhordarian

That's amazing. That's amazing. Dr. Nissen, your contributions to cardiology has been unparalleled and thank you so much for sharing your results of this amazing trial and congratulations.