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A Turning Point for Lipoprotein(a) Treatment: Are Clinical Laboratories Ready?

Article:
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Guest: Leslie Donato is a clinical chemist and associate professor in the Department of Laboratory Medicine and Pathology at Mayo Clinic in Rochester, Minnesota.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett.

What if I told you that there's a lipoprotein that's more atherogenic than LDL cholesterol, is expressed at high-risk concentrations in 20% of the world's population, and whose measurement is recommended by international cardiovascular risk guidelines? And what if I followed that up by sharing that this lipoprotein is measured in less than 5% of patients?

You'd likely think that it's either the worst publicized test in all of laboratory medicine or that there are some serious challenges preventing its widespread implementation. As is often the case, it's a combination of the two. The particle in question is lipoprotein(a), a very strong predictor of lifetime cardiovascular risk that is woefully underutilized due to a combination of limited effective treatments and inherent complexities that make accurate measurement difficult.

Recent advancements addressing both those limitations are now flipping the script and have Lp(a) poised to become a staple of cardiovascular risk assessment. A perspective article in the February 2026 issue of *Clinical Chemistry* describes the association between Lp(a) and cardiovascular risk, explains why it's a particularly challenging analyte to measure, previews new targeted therapeutics, and summarizes the impact of all of this on clinical laboratories.

Today, we're joined by the article's author. Dr. Leslie Donato is a clinical chemist and associate professor in the Department of Laboratory Medicine and Pathology at Mayo Clinic in Rochester, Minnesota. She is a recent recipient of the Cooper Award from the ADLM Lipids and Lipoproteins Division for her contributions to the field. So, Dr. Donato, let's get started with the basics. We've been hearing a lot about lipoprotein(a) lately. For those who may not be familiar, can you give us some background on this lipoprotein?

Leslie Donato: Sure, yes, I'd be happy to. So lipoprotein(a), or Lp(a), is an apoB family member of lipoproteins. It's unique to the other

more well-known apoB-containing lipoproteins such as VLDL or LDL, in that it contains a unique apolipoprotein called apo(a), which is covalently bound to the apoB moiety of the particle. Now, apo(a) protein is fascinated because of several factors. First, the protein sequence shows homology to plasma antigen. It has an inactive protease domain and other homologous sequences, specifically several different kinds of kringle domains. That leads to the second interesting fact about the Lp(a) that even though these kringle domains are present in only one copy in plasminogen, somehow one of the kringle domains in the apo(a) gene [*LPA*, lipoprotein(a)] is found in variable numbers of repeats.

So, the number of kringle IV_2 domains is reported to vary from one to more than 40 copies in the apo(a) gene, dependent on which allele is inherited in that individual. Therefore, the size of the apo(a) protein is highly variable within our population and correspondingly, the size of the Lp(a) lipoprotein particle that we're talking about today vary substantially as well from about 300 to about 800 kilodaltons.

So interestingly, while the synthesis of Lp(a) is incompletely understood, it's known that the circulating concentration of Lp(a) is mostly determined by the genetic expression of the gene encoding for that apo(a) protein. So that's the Lp(a) lipoprotein itself.

Let's talk about its function. I don't know anything good or beneficial that Lp(a) does for our bodies. The particle is highly pro-atherogenic. Just like its well-known cousin LDL, Lp(a) carries cholesterol cargo and can transverse the arterial wall where it contributes to atherogenic plaque buildup. It's also been shown to carry oxidized phospholipids, which is another key mediator of the lipoprotein's pro-atherosclerotic actions.

Lastly, because of the presence of the inactive protease domain, Lp(a) may compete for substrate binding with plasminogen and contributes to prothrombotic phenotypes.

So given all of these biological contributors, Lp(a) has been shown to be directly and causally associated with increased risk for cardiovascular disease, such as heart attack and stroke, and elevated concentrations are also associated with increased risk for calcific aortic stenosis. Importantly, the higher the Lp(a) concentration is in circulation, the higher the risk for these outcomes.

Bob Barrett: How does cardiovascular risk from Lp(a) compare to other better-known cardiovascular risk agents, such as LDL cholesterol?

Leslie Donato: Yes, the comparison is interesting. LDL and Lp(a) share a lot of similarities. Their overall size and density is very similar. They both contain apolipoprotein B and carry cholesterol cargo. However, LDL is typically measured via LDL cholesterol and the lipid panel is highly modifiable via lifestyle modifications such as diet and exercise and pharmacotherapies such as statins or PCSK9 inhibitors, etc.

Conversely, concentrations of Lp(a) are quite resistant to change because they are mostly derived from genetic expression of apo(a). Therefore, the circulating concentrations are really quite stable and do not change much in adulthood. Also interesting, data from the UK Biobank has recently shown that Lp(a) is actually six times more pro- atherogenic on a per particle basis compared to LDL. Now, of course, we should remember that there are actually much more LDL in circulation on a molar basis compared to Lp(a), but Lp(a) is a much more potent progenitor of atherosclerosis compared to LDL.

Now, importantly, recent data from the Women's Health Study has actually shown a one-time measurement of either LDL cholesterol or Lp(a) is predictive of future cardiovascular events for up to a staggering 30 years and the predictive power increases when combining both of those values together.

Bob Barrett: That's very interesting. So why is Lp(a) being talked about so much by lipid and cardiovascular risk experts?

Leslie Donato: Yes, now we're getting into the topic of this perspective article. In current clinical practice, there are no approved pharmacotherapies that specifically target Lp(a). Now, that does not mean that there's no way to lower cardiovascular risk in people that are high Lp(a) expressors. The current strategies involved overall risk lowering of modifiable risk factors such as optimization of lifestyle behaviors such as proving diet and exercise, smoking cessation, and stress reduction. Additionally, aggressive lipid lowering therapies of lipids that are modifiable when possible through pharmacological agents is recommended.

And some of those modifying therapies such as PCSK9 inhibitors do modestly lower Lp(a), but only by about approximately 20 to maybe up to 30%. For patients that express the highest concentrations of Lp(a), lipoprotein apheresis is actually an approved treatment and can provide time average to Lp(a) lowering, but of course apheresis therapy is very time-consuming and not available to many individuals. However, we should know that the mainstay of lipid lowering therapy statins has been shown to be ineffective or can actually even slightly increase Lp(a) circulating concentrations. But that treatment landscape is hopefully

about to be dramatically improved for patients that express high concentrations of Lp(a).

New pharmacotherapies in clinical trials have shown to dramatically lower Lp(a) concentrations and are anticipated to lower overall cardiovascular risk. This new class of treatments utilize nucleic acid-based therapies, either antisense oligonucleotides, or small interfering RNAs. They are subcutaneously injected molecules that disrupt the synthesis of that apo(a) protein in the liver. The result is a drastic reduction in synthesis of apo(a) and a corresponding reduction in blood concentrations of Lp(a), the lipoprotein that we're talking about today.

The amount of that reduction being reported is on the order of 80, 90, or even 95% reduction in blood concentrations of Lp(a) at the highest doses for the various pharmaceuticals currently in clinical trials. The one I wrote about here is an siRNA therapy called lepodisiran by Eli Lilly. However, similar significant reductions have been reported by other agents and trials, such as olpasiran by Amgen, zerlasiran by Silence Therapeutics, and pelacarsen by Novartis.

These results are markedly better than the reduction seen by currently available treatments, such as the PCSK9 treatments I mentioned earlier. All of that is very exciting. Of course, the real question is whether these impressive Lp(a) lowering data will translate into lowering of cardiovascular events in people that are high Lp(a) expressors. The first outcomes from Phase III trials are expected to be reported later this year.

I will say the anticipation of these outcomes are palpable in cardiology and lipid clinic practices as well as their national meetings. There's a lot of hope that these trials will show a benefit to these patients.

Bob Barrett: Well, this does sound very important for those patients that express high concentrations of Lp(a). What could you tell us about laboratory testing for Lp(a)?

Leslie Donato: Yes, the laboratory plays a critical role here. We have to accurately measure Lp(a) in patients so that these individuals that express high concentrations of Lp(a) are identified. Currently available testing involves immunoassays that detect the apo(a) protein on the Lp(a) lipoprotein. So these assays are specific for Lp(a) and do not cross react to other lipoproteins, and there are available reagents available on automated immunoassay platforms that are in most clinical laboratories.

Most of these assays use polyclonal antibodies. The reason polyclonal antibodies are used is because historically it's been

very challenging to make monoclonal antibodies to apo(a) because of the highly repetitive nature of the peptide sequence. But the use of polyclonal antibodies, as we can probably appreciate, introduces a challenge to correct measurement of Lp(a) because of the heterogeneous size of the Lp(a) particles. With different numbers of kringle repeats in the apo(a) protein comes different number of antigen binding sites when using polyclonal antibodies.

Therefore, we know these assays can be susceptible to bias. Either a positive bias or a negative bias, depending on the number of kringle domains present in the patient sample, compared to the calibrators used in the assay. Assay manufacturers try to mitigate that bias as best they can by designing calibrators with mixes of different apo(a) isoform sizes and incorporating multiple levels of calibrators. But to a certain degree, assay bias still exists in all Lp(a) assays.

Therefore, it's been recommended that assays be calibrated in molar units rather than mass units to more accurately reflect the true concentration of Lp(a). And we should recognize that historically, Lp(a) assays have been calibrated in mass base units. Those are those that are reported out as milligram per deciliter. And most outcome studies and population surveys have been reported in those mass units. But newer assays calibrated in molar units are now available and more studies are reporting how to use these assays in clinical practice.

Bob Barrett: Dr. Donato, are there recommendations for what tests physicians and laboratories should utilize and how to interpret those results?

Leslie Donato: Yes, there are recommendations. Because the assays that measure in molar units are slightly better in mitigating the bias caused by isoform size, it is recommended to use an assay calibrated in molar units if one is available to your hospital system. However, it's also been shown that one should not convert results obtained in mass units to results in molar units because it actually that conversion process introduces more in accuracy than the original bias in the mass assay. So if you only have access to Lp(a) results in mass units, use those results and interpret using the specific clinical cut points for mass units in milligrams per deciliter.

Speaking of interpretation, we know that statistically significant risk starts with an Lp(a) concentration at either 30 milligrams per deciliter if you're using an assay calibrated in mass units or 75 nanomoles per liter if using an assay calibrated in molar units. It is recommended to start flagging results in the clinical records starting at those values. We know that cardiovascular risk increases as Lp(a) concentration increases and clinical guidelines may use

variable cut points for patient decision making based on the clinical context of the patient.

Bob Barrett: Doctor let's get back to the ongoing Phase III clinical trials. What if any impact will the results from those clinical trials have on clinical laboratories?

Leslie Donato: Yeah, good question. We don't know for sure but I and many others anticipate a dramatic increase in demand for Lp(a) testing. We in my clinical practice are already seeing a significant increase in our monthly Lp(a) orders over the last year as awareness of the Phase I and II trial data increases and I don't say this lightly but the wave of demand for this test could more resemble that of a tsunami.

The reason I say this is based on looking at current testing rates now and projecting to the future. Based on epidemiological data we know that approximately 20% of individuals on this planet express concentrations of Lp(a) that put them at elevated cardiovascular risk. So let me say that a different way.

Out of 8.2 billion individuals on this planet, a full 20% of them are at increased cardiovascular risk because they express elevated Lp(a). However, we also know and it's been reported that test utilization of Lp(a) in clinical practice is extremely low.

One recent study found that within a large academic health system in California, out of 5.5 million adults seen over a 12-year time span, only 0.3% of them had an Lp(a) order test anywhere in their medical chart. The rates for testing increase in special groups like those with a strong family history of cardiovascular disease or in patients that had a previous heart attack themselves but even then the testing rates never topped 6%. So importantly, current United States multi-society guidelines from the American Heart Association and American College of Cardiology and others list Lp(a) as a risk enhancer to be considered in certain circumstances like those with intermediate risk or a strong family history of disease, etc.

However, it's noteworthy to observe that many other international guidelines, for example those in Europe and Canada and many others, are now endorsing once per lifetime testing for all adults. Similarly, the National Lipid Association here in the US also recommends testing Lp(a) in everyone. So if these trials are beneficial giving physicians a first ever tool to specifically treat and lower cardiovascular risk in persons with elevated Lp(a) and our clinical colleagues start following recommendations for testing Lp(a) in everyone, we are likely going to see a huge increase in Lp(a) testing demand in our clinical laboratories.

Bob Barrett: Well, finally Dr. Donato, if your sounds like demand for Lp(a) testing is likely to see a dramatic increase, do you have any last comments for laboratories that are either currently performing the test or are considering implementing the test in the future?

Leslie Donato: Yes, we know that many of our clinical colleagues, especially those in general practice, may be unfamiliar with Lp(a) and the risk that it poses to those that express it at high concentrations and because Lp(a) is not included in the basic lipid panel, there is no way to identify a person as a high Lp(a) expressor unless the immunoassay test is ordered. We would do well to understand this unique biomarker of cardiovascular risk, get familiar with the challenges for accurate testing in the laboratory, advocate for awareness of our patients and practice groups, and lastly, given the very look testing rates we see in clinical practice, I would say don't get too caught up on which assay is being used at your institution or your reference laboratory.

Yes, molar unit assay is slightly more accurate, but testing is better than not testing, so utilize the test at your disposal. If we do that, we could play a significant part in identifying the millions of individuals that are currently unaware that they express high Lp(a) concentrations and we can identify those that are at increased risk for future cardiovascular events so that their risk can be mitigated as early in life as possible.

Bob Barrett: That was Dr. Leslie Donato from Mayo Clinic in Rochester, Minnesota. She wrote a perspective article in the February 2026 issue of *Clinical Chemistry* highlighting the increasing importance of Lp(a) measurement, and she's been our guest in this podcast on that topic.

I'm Bob Barrett. Thanks for listening.