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JCL Roundtable: Global Think Tank on Lipoprotein(a)

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Abstract: Lipoprotein(a) operates in causal pathways to promote atherosclerosis, arterial thrombosis, and aortic stenosis. It has been associated with rare cases of nonatherosclerotic arterial thrombotic stroke at any age. Inherited variation of lipoprotein(a) levels substantially increases cardiovascular risk in 20% of people worldwide. Recent progress in identifying the risk associated with lipoprotein(a) and in pursuing effective treatment has led to a recent Global Think Tank including representatives from the European Atherosclerosis Society, American Heart Association, Preventive Cardiovascular Nurses Association, National Lipid Association, and other groups. The need for standardized laboratory measurement in nanomoles per liter met with unanimous consensus. Atherosclerotic risk is linearly associated with plasma lipoprotein(a) levels, so that persons with the highest levels may have risk similar to other severe inherited lipoprotein disorders. Universal once-in-lifetime screening has been recommended by European and Canadian cardiovascular societies, but not by U.S. organizations. Current pharmacologic therapies are limited to 20-30% lowering of lipoprotein(a) levels, and no pharmacologic treatment for lowering lipoprotein(a) has yet been proven to reduce risk in a cardiovascular outcomes trial. Treatment for high-risk patients focuses on reducing low density lipoprotein cholesterol and other risk factors. New therapies targeting messenger RNA for apolipoprotein(a) can achieve 80-90% reduction of lipoprotein(a) levels. One such therapy using a liver-directed antisense oligonucleotide is currently being tested in a large cardiovascular outcomes trial. Increased recognition of lipoprotein(a)-associated risk and emergence of potentially effective therapy together lead to a mandate for a unified global effort on education, standardization, and clinical management.
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JOHN GUYTON, M.D.: This JCL Roundtable derives from a recent Global Think Tank on the emerging risk factor, lipoprotein(a). In 1963 Kåre Berg in Oslo, Norway, identified by antibody screening in rabbits a serum component that he characterized as a lipoprotein. He called it the Lp(a) antigen, later transmuted to lipoprotein(a). It's an odd name for a lipoprotein, but consistent with its discovery through immunology.

In 1972, Gösta Dahlén and Curt Furberg in Boden, Sweden, reported that a distinct pre-beta lipoprotein ("split prebeta") was associated with coronary heart disease. Within 2 years, Dahlén, Berg, and colleagues recognized that their lipoproteins were the same. Through the next 2 decades a succession of papers confirmed that lipoprotein(a) is a strong genetic risk factor for atherosclerotic cardiovascular disease.

By 1989 Gert Utermann after a series of laboratory and clinical studies wrote a memorable review in Science titled "The mysteries of lipoprotein(a)". As we move into our discussion, you'll find that lipoprotein(a) remains mysterious today in several ways. Yet much has been learned.

Structurally lipoprotein(a) [Lp(a)] resembles low-density lipoprotein (LDL), having a neutral lipid core rich in cholesteryl ester, a surface monolayer composed of phospholipids and cholesterol along with apolipoprotein B (apoB), and additionally a large glycopeptide, apolipoprotein(a) [apo(a)] covalently attached to apoB by a disulfide bond. In routine laboratory measurements Lp(a) lies hidden as an unrecognized subfraction of LDL cholesterol, often just 1 to 8 mg/dL in its cholesterol content but sometimes much more. The gene for apo(a), called *LPA*, is homologous with the plasminogen gene, sharing 2 of the 5 plasminogen kringle motifs. Three disulfide bonds within each kringle create a structure that resembles the namesake Danish pastry. Unlike plasminogen, apo(a) has no potentially active protease domain. Kringle IV in apo(a) has 10 subtypes arranged sequentially, and subtype 2 exhibits genetic hypervariability with 3 to 43 repeats. *LPA* alleles with few repeats are associated with higher levels of Lp(a) in circulating blood.

Because apo(a) and plasminogen share a kringle subtype with high affinity for a binding site on fibrin, Lp(a) can interfere with the fibrinolytic activity of plasminogen/plasmin. This and other properties endow Lp(a) with procoagulant potential expressed in the arterial circulation, but minimally or not at all in the venous circulation.

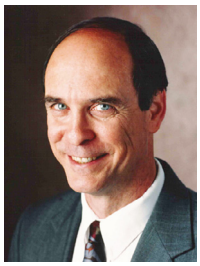
By 2005 Sam (Sotirios) Tsimikas, Joe Witztum, and others added to the Lp(a) story by identifying oxidized phospholipids covalently attached to lysines on kringle V. Oxidized phospholipids can induce inflammatory responses and are also associated with development of coronary atherosclerosis.

That's the backdrop for the clinical Global Think Tank on Lp(a) convened in November 2020. We are privileged to have 4 participants from that virtual group session to discuss ongoing science and clinical implications. Lisa Maher, DNP, ARNP, comes to us as a Board Member of the Preventive Cardiovascular Nurses Association here in the U.S. Eduardo Sanchez, MD, MPH, is the Chief Medical Officer for Prevention of the American Heart Association. Prof. Lale Tokgözoğlu, MD, FACC, FESC, practices preventive and clinical cardiology at Haceteppe Faculty of Medicine in Ankara, Turkey, and is immediate Past President of the European Atherosclerosis Society. Jamie (James) Underberg, MD, runs the Lipid Clinic at New York University Langone Health and has served as President of the National Lipid Association.



Dr. Sanchez, could you tell us about the purpose of the Global Think Tank on lipoprotein(a)?

EDUARDO SANCHEZ, MD, MPH: Absolutely, and I'm so pleased to be a part of this roundtable. The Global Think Tank, I think put quite simply, was to bring the perspectives and the participation of a variety of organizations who recognize that lipoprotein(a) can be an important part of assessment and treatment of patients. But we were speaking with slightly different voices about this. The idea is to come together to try to align our voices around measurement, risk assessment, and therapy.



DR. GUYTON: I see. It's time to bring Lp(a) forward as a risk factor and possibly a treatment target. But what are the risks of high Lp(a)?

LISA MAHER, DNP: Sure. There are risks definitely associated with Lp(a). Some of the risks we talked about during the Think Tank were specifically the increased risk for atherosclerosis, the increased risk for aortic valve disease, and then the risk associated with stroke. Specifically, risk of stroke not only among older adults, but also among children and premenopausal women.

DR. GUYTON: We don't ordinarily think about children or premenopausal women being at risk for stroke, but rare events happen, and sometimes in association with high levels of Lp(a). What about the risk for atherosclerosis? Can someone amplify that?

DR. SANCHEZ: I'm happy to jump in. There's at least a two-fold increase in atherosclerosis with high lipoprotein(a). It's a critically important consideration in trying to assess risk for atherosclerosis and what to do about it.

DR. GUYTON: And perhaps 5% to 10% of the worldwide population have Lp(a) levels high enough to double their risk of atherosclerotic cardiovascular disease. Dr. Tokgözoğlu, could you tell us a little bit more about the aortic valve?

PROF. S. LALE TOKGÖZOĞLU, M.D.: Yes. We know that aortic valve stenosis is seen more frequently in patients with high Lp(a) levels, and also faster progression of aortic valve stenosis has been shown in patients with high Lp(a) in the ASTRONOMER trial. I would like to also add that recent observational data from two Danish registries in 70,000 subjects showed that high Lp(a) was an independent predictor of total and cardiovascular mortality, but not non-cardiovascular mortality.

The INTERHEART study, which is one of the largest cross-sectional studies looking at the risk of myocardial infarction all over the world, showed that Lp(a) concentration above 50 mg/dL was associated with an increased risk of myocardial infarction, independent of established cardiovascular risk factors.

Finally, Lp(a) is not only a risk factor for the first event, but also for recurrent events. This has been demonstrated recently not only in Danish registries, but also in the two large outcome trials with PCSK9 inhibitors, FOURIER and ODYSSEY outcomes, showing that high levels of Lp(a) were associated with an increased risk of recurrent events in patients who already have atherosclerotic vascular disease.

DR. GUYTON: So it's a wide-ranging risk factor for cardiovascular disease, well documented. But some risk factors operate in a causal pathway, and some do not.



DR. TOKGÖZOĞLU: Mendelian randomization studies have clearly shown that genetic variants in the Lp(a) locus regulating Lp(a) levels are robustly associated with coronary heart disease risk in a linear and dose-dependent fashion.

DR. GUYTON: So Mendelian randomization confirms the epidemiologic studies and also establishes Lp(a) mechanistically as causative.

What about the distribution of Lp(a) levels? Who has high levels, and does it differ by ethnicity? I'll come back to you, Dr. Tokgözoğlu, to introduce us to that topic and then ask Dr. Underberg also to comment.

DR. TOKGÖZOĞLU: The distribution of the Lp(a) is skewed in the population towards the left. We know that 20% or so of the population has Lp(a) levels above 50 mg/dL, so this is not a small number we are talking about. The distribution is bell shaped in Blacks, who also tend to have higher Lp(a) levels. Women usually have slightly higher levels than men.

DR. GUYTON: I can't help telling you about my first venture into clinical research. Gösta Dahlén came from Sweden to join us at Baylor College of Medicine in Houston, where I was working, and we also met Dr. Tokgözoğlu who was there for some time. Dahlén was examining a split pre-beta band on lipoprotein electrophoresis that he found to be common among renal patients on dialysis. But we knew even then that African Americans are more susceptible to kidney disease. We looked, and almost all our dialysis patients in the sample were Black.

So Dahlén and I decided to gather employees of Methodist Hospital, Black and White, to compare their Lp(a) levels. The White volunteers showed the expected skewed distribution, but the Blacks had more of a bell-shaped Lp(a) distribution. We now know that the median Lp(a) level in Blacks is 3 times as high as it is in Whites.

DR. GUYTON: Dr. Underberg, I think you have something to add.

JAMES UNDERBERG, M.D.: That's true. I think that the information about Lp(a)-associated risk is changing, which is what's so interesting about this space. We had for a very long time thought that it was a very binary decision point with Lp(a), that once you were above a threshold level, your level was elevated and associated with ASCVD risk.

But recently published data suggest that the relationship of Lp(a) levels to cardiovascular risk is linear. This linear association of risk is one that is found among all of the different ethnicities and between male and female sex.

What's also interesting is that the association of risk seems to be greater in those without atherosclerosis than those with pre-existing disease. The predictive value is greater. Like everything else, the space continues to change and evolve. Dismissing mild elevations is probably not something that we should be doing anymore.

DR. GUYTON: Of course, pre-existing disease itself is a risk factor, and perhaps some of the risk associated with Lp(a) is already incorporated into the risk ascribed to pre-existing disease.

DR. UNDERBERG: Exactly.



DR. GUYTON: Up to now I have given little attention to the linear relationship with risk. Most of us have seen Lp(a) levels ranging from less than 10 nmol/L to almost 400 nmol/L. A recent report suggested that if you have an extremely high Lp(a) level, your risk of atherosclerotic cardiovascular disease may be equivalent to having familial hypercholesterolemia, which is an astonishing thing to me. Yet that's the implication of the linear relationship with risk.

As long as we're thinking about the distribution and risk of Lp(a), I'll push Dr. Underberg to the limit with the next question. Do people need a certain amount of Lp(a) circulating in the blood? What is it good for?

DR. UNDERBERG: Well, since we don't really understand what Lp(a) does, I would tell you that right now the thinking is that we don't really need it. Having a low level is not something to be concerned about.

DR. GUYTON: Right. Most people have very little Lp(a) circulating in their bloodstream. It's reminiscent of a surprise we had in the 1990s when John Dietschy and Stephen Turley showed how little we know about the physiological role of LDL itself.

DR. UNDERBERG: Exactly.

DR. GUYTON: There's speculation that prehistoric humans experienced much more physical trauma, cuts and bruises constantly, and perhaps wound healing was helped by higher Lp(a) levels. It's not that patients with high Lp(a) today have any better propensity to heal surgical wounds. But perhaps there were evolutionary pressures in prehistoric times that are no longer part of our lives today, and now we don't really need Lp(a) at all.

I understand that one highlight of the Global Think Tank was agreement on measurement of Lp(a). Certainly, antibody-based assays are standard, and we no longer rely on Dahlén's split pre-beta, or Jere Segrest's ultracentrifugal technique known as vertical autoprofile, or sinking pre-beta which combined ultracentrifugation and electrophoresis – though all of those helped to define the structure and role of Lp(a).

But the Global Think Tank came to a conclusion about this and really put the standard of measurement on the map as a central issue for discussion today. Dr. Sanchez?

DR. SANCHEZ: I think this is one place where there was unanimity. Not that there wasn't in others, but this is one where there was quick unanimity. Standard measurement is really important, and nanomoles per liter as the unit of measurement is the consensus.

There are global efforts to standardize assays for determination of Lp(a) levels. That's being led by the World Health Organization. The Centers for Disease Control is involved in the United States, as well as the Federation of Clinical Chemistry and Laboratory Medicine. Let's all use the same units of measurement and a standardized assay. That was felt to be really important not only for clinical care, but also for research, so that what we're gleaning from research can be more immediately applied to the clinical context.

DR. GUYTON: I will second that. At my institution, Duke University, we're still using the milligrams per deciliter (mg/dL) mass concentration (total lipoprotein mass, not cholesterol mass). Santica Marcovina, Sam Tsimikas, Marlys Koschinsky, and other experts have made it clear that you can't convert directly between mg/dL and nmol/L, mostly because of varying mass of apo(a). So how can we move forward to implement this recommendation to standardize the way we measure Lp(a)?



DR. MAHER: During the Think Tank, we talked a lot about how to make our recommendations known. A key takeaway was education not just to fellow clinicians, but also to patients and to laboratory services. We found that one barrier is that much current research still reports Lp(a) in mg/dL. We talked about the costs associated with making the change to nmol/L as well, because there is a significant cost associated with making a clinical recommendation to screen Lp(a). With that, we talked about the cost barriers, not just the cost of the test, but also the downstream costs of follow-up and future therapy.

In going forward, we looked at the importance of collaborations with different laboratory services and achieving standardization. Also going forward, we looked at the possibility of group consensus and payors driving that payment based on recommendations from professional organizations.

DR. GUYTON: Should we consider specific cutpoints for various ethnicities to define the risks associated with Lp(a). If yes, what would those cutpoints be? Dr. Sanchez, do you think we're ready for that?

DR. SANCHEZ: I think we're ready to continue talking about it. Cutpoints by race and ethnicity may be less of an issue in Europe–I wouldn't say not an issue at all–than in the United States, where there is much demographic diversity in the population that will continue shifting over time to lower percentages of White Americans, slight increases in percentages of Black Americans, and growing percentages of Latino/Hispanic Americans, and Asian Americans in general. This was a point of focused discussion of the Think Tank. This is an area where the consensus was that the evidence is emerging and just as we talked about, even just weeks to months later — there are new observations. There probably should be cutpoints to define risk by race/ethnicity; however, we're not quite ready for primetime with cutpoint recommendations.

DR. GUYTON: Yeah. I agree that we have to be careful about it. Often we see the reference level for Lp(a) as less than 75 nmol/L, but we have to remember that it's around the 70th percentile of the population, so we're going to be getting concerned about a lot of people. The 80th percentile is around 100 nmol/L according to the National Lipid Association Statement, and the 2018 AHA/ACC/Multisociety Guidelines assigns >125 nmol/L as a marker of high risk.

I'll turn to Dr. Underberg again. Does everyone with a high or very high Lp(a) level have substantial cardiovascular risk?

DR. UNDERBERG: When we're talking about populations, obviously as lipoprotein levels increase, risk for ASCVD events in the population also increases. But just like other biomarkers, there are many people who have elevations in Lp(a) who do not develop ASCVD or any of the other endpoints that we've been discussing today. It needs to be personalized for the individual patient.

Certainly, the context of family history is one of the things that often becomes very important in assessing the importance of elevations in Lp(a). That's something that's actually been highlighted in statements by both the European Atherosclerosis Society and the National Lipid Association.

DR. GUYTON: Thanks. Let me ask Dr. Maher and Dr. Tokgözoğlu next: Should everyone be screened at least once in their lifetime for elevated Lp(a) levels? And is once enough? What are the benefits and costs of that? I don't want

to get us in trouble with the United States Preventive Services Task Force, but what are your personal opinions?

DR. MAHER: Yes, just because of the prevalence, I agree with screening. Approximately 20% of the population have elevated morbidity and mortality risk from Lp(a). This brings up many different topics including cascade screening and a genetic component. If one family member has been shown to have increased risk from Lp(a), do we then continue to screen other family members? Non-genetic factors can also increase Lp(a). Chronic kidney disease, hypothyroidism, and, in women, menopause tend to elevate Lp(a).

I like the idea of screening because I am someone that, if the levels are elevated, I want to do the best I can as a clinician to help treat and raise the awareness of the importance of Lp(a).

DR. TOKGÖZOĞLU: I think optimally everyone should be screened at least once in a lifetime for elevated Lp(a). The high prevalence of elevated Lp(a), the strength of association with disease, and the potential to improve cardiovascular risk stratification justifies this universal screening approach.

Here in Europe we recommend in our guidelines universal screening. The recent Canadian guidelines also agree that everyone should be screened. If universal screening is not feasible for economic or other reasons, we should at least try to measure Lp(a) in patients who are likely to have high Lp(a), like those with premature cardiovascular disease history in the family, those with familial hypercholesterolemia, those who have recurrent events despite statin use, and also if we want to reclassify risk in high- or intermediate-risk patients.

DR. GUYTON: That's very helpful.

DR. UNDERBERG: I'll just jump in on this and say that I agree with these thoughts. The National Lipid Association statement did not make the leap that our European colleagues have made in recommending universal screening. I think part of it related to concerns about cost and availability of effective therapeutic options. As we have pointed out, because of the importance of Lp(a) as a risk factor–and we're going to get into therapeutic approaches–it certainly may modify how you address other risk factors.

I understand why my NLA colleagues did not make the recommendation, but I believe it's not unreasonable to think about screening everyone at least once.

DR. GUYTON: We know that LDL rises as people age through their early decades until mid-adult life, about age 45 in men and about age 55 in women. But Lp(a) levels are very constant throughout a person's life. The lipoprotein level is 80% to 90% genetically determined. It's not subject to much dietary regulation, as other lipoproteins are. Once you have a single reliable measurement of Lp(a), you can pretty well trust it. Maybe if you're surprised and say, "Was it the wrong tube of blood?", you check it again. But generally, one single lifetime test would be enough.

Now a practical question. How can we manage patients with elevated Lp(a)?

DR. MAHER: I think the first goal that we need to think about is how to push the LDL level lower. In screening patients, we want to think about screening those with family history of premature ASCVD, males less than age 55 and females less than age 65. We want to think about primary hypercholesterolemia with LDL cholesterol levels greater than 160 mg/dL, metabolic syndrome, chronic kidney disease, chronic inflammatory conditions, and premature menopause.

Statin therapy can lower LDL, but can initially raise Lp(a) levels. Some studies have shown up to 11% increase, but further studies are warranted. Patients on statin therapy who have very high Lp(a) levels sometimes will have a lower response to statin therapy. Despite the increase in Lp(a) with statin use, statins clearly remain beneficial to patients with elevated Lp(a) levels, and they should be encouraged to continue with statin treatment. Consideration should also be given newer options, such as PCSK9 inhibitors.

DR. UNDERBERG: As I mentioned earlier, current thinking is to view elevated Lp(a) as a risk factor for ASCVD. In fact, in the most recent iteration of the AHA/ACC/Multisociety Guidelines here in the United States, similar to global thinking, it's listed as a risk-modifying factor. When elevated, it means you need to be more aggressive about risk reduction across the board in any patient with elevated Lp(a). Obviously, as Dr. Maher mentioned, one important component of that is lowering LDL.

A caveat that we haven't really discussed here is that many of the agents we use to lower LDL do not lower Lp(a). In fact, a blunted response to LDL lowering with either statins or ezetimibe and possibly even PCSK9 inhibitors can be a warning sign that Lp(a) may indeed be elevated, if it hasn't been measured in that patient.

PCSK9 inhibitors lower Lp(a) 25% to 30%, depending on which data set you're looking at. Certainly, there's some suggestion in post hoc analyses of the two PCSK9 inhibitor trials, that the incremental Lp(a) lowering in the patients in the highest quartiles may provide some additional benefit.

Just as important as LDL lowering is addressing unhealthy lifestyle, overweight and obesity, smoking, inactivity, healthy diet management, blood pressure management, management of blood sugar, etc. It's really an across-the-board alert that we need to address risk aggressively.

DR. TOKGÖZOĞLU: I fully agree with my colleagues that we should recommend earlier and more intensive lifestyle and risk factor modification in these patients, and try to get to guideline-recommended goals for LDL cholesterol and other risk factors as much as we can. Here in Europe, we recently updated the dyslipidemia guidelines and have even more stringent goals for high-risk patients.

In secondary very high-risk prevention, in addition to lowering LDL cholesterol by at least 50% from baseline, we're also recommending a goal of getting to less than 55 mg/dL. If we're unable to do that with statins and ezetimibe, we recommend using PCSK9 inhibitors, which also moderately lower Lp(a) levels.

In addition to all this, we know that apheresis can significantly decrease Lp(a) levels. Throughout Europe, apheresis is mostly used to lower LDL in patients with familial hypercholesterolemia. However, in Germany, high Lp(a) and progressive atherosclerosis despite other medical therapies is an

indication for apheresis, and they have quite a lot of experience there in terms of lowering Lp(a) with apheresis.

DR. GUYTON: Great discussion. Interestingly, Dr. Patrick Moriarty led a group to the Food and Drug Administration, and lipid apheresis is now approved for high Lp(a) in the United States as well, when there is persistent and progressive atherosclerotic disease, usually coronary heart disease, and LDL-C remains above 100 mg/dL and Lp(a) with the old units above 60 mg/dL. Otherwise, Lp(a) is very hard to reduce substantially. There are no dietary treatments. Interestingly, saturated fat will lower Lp(a) somewhat, but it promotes atherosclerosis overall. The androgenic steroids that weightlifters abuse will lower Lp(a), but that comes with terribly high cardiovascular risk.

The options that we have for dealing with Lp(a) itself are limited, but a new treatment is "on the horizon," so to speak. Can someone tell us about that?

DR. UNDERBERG: Like everything else in our lipid space, we're moving ahead at breakneck speed. It's an exciting time to be a lipid specialist. There are several treatments currently in clinical development. One technology that I think many of us are familiar with is antisense inhibition. This is a small snippet of oligonucleotide, a modified form of nucleic acid, that finds its way into the cell and creates a duplex strand with the messenger RNA that codes for the production of apo(a), the specific protein component of Lp(a).

When this duplex strand is created, an enzyme called ribonuclease (RNase) identifies it as abnormal and breaks down the particular component that has been targeted by the antisense oligonucleotide. What's very interesting is these drugs have been tailored so that the antisense oligonucleotide is not degraded by RNase, and it can essentially bind to another piece of messenger RNA. By degrading the mRNA that codes for the production of apo(a) protein, the production of Lp(a) is inhibited. This effect lasts for several weeks at a time. The antisense oligonucleotide has been modified over time and developed into a more targeted therapeutic with the addition of certain other moieties attached to it, particularly one called GalNAc, which allows it to be directed to the liver. Thus it can be more effective at lower doses with better side effect profile.

One of these drugs called pelacarsen has demonstrated significant efficacy, up to 90% lowering of Lp(a) in phase 2 trials. There's now a phase 3 outcomes trial going on in patients with pre-existing ASCVD looking at lowering Lp(a) and preventing future cardiovascular events. This trial is enrolling now, and it's very exciting. You have to lower Lp(a) a significant amount to see benefit, and so the 80% to 90% reduction seen with pelacarsen is appropriate for this trial.

DR. GUYTON: So that's the oligonucleotide. You mentioned another pharmaceutical approach. Is it small interfering RNA?

DR. UNDERBERG: Exactly. The small interfering RNA technology works via a RNA-induced silencing complex (RISC) mechanism. Its effect actually lasts for even longer than antisense technology and essentially turns on cellular machinery to target the specific messenger RNA that codes for apo(a).

DR. GUYTON: Welcome to the world of RNA biology and pharmacology.

DR. UNDERBERG: It's fascinating.

DR. GUYTON: It's revolutionizing a number of fields, and it offers the chance to get 80% to 90% reduction of Lp(a). And because most people have those very low levels anyway, this kind of reduction appears to come without risk.

Dr. Sanchez, what resources would be most beneficial for clinicians in the diagnosis and potential treatment in patients with elevated Lp(a)? What organizational resources do we need in a public health sense?

DR. SANCHEZ: Clinicians could benefit from guidelines that more clearly call out lipoprotein(a) risk, assessment, and management, consistent with the current science as discussed in our Think Tank meeting, and with the commitment to update periodically as the science evolves – including consensus on standardized measurement, cutpoints as we discussed earlier, and new insights on management – even treatment protocols embedded in guidelines.

Guidance at a health systems level, both governmental and non-governmental, would be beneficial to assure that Lp(a) testing is equitably accessible, affordable, and utilized. Health systems should be expected to track utilization and use data for patient care and systems process improvements. There should be monitoring across health systems. We would want to avoid any unintended healthcare disparity that might exacerbate existing health disparities. For a number of reasons, we should worry that we could see variability in utilization by sociodemographics (race/ethnicity; insurance status; income; educational attainment) rather than by clinical presentation – potentially different risk cutpoints notwithstanding.

Guidance for payors should address the value proposition of Lp(a) testing – why the test is "valuable" clinically and economically.

Guidelines generally inform the "why" and "what" should be done, but we need to be mindful of the "how" we get it done as we proceed forward, for many of the reasons that we talked about before. There's still new science emerging. There is not consensus around universal screening. How do we build our consensus about the role and importance of universal screening? — the why. Then how do we logistically perform and track that once-in-a-lifetime test in a systematic way? Guidelines and guidance will be critically important for helping clinicians, health systems, and payors know why and what to do related to Lp(a) and then how to do it.

DR. GUYTON: A great overview. Dr. Maher, what are the potential barriers that you see to implementing the kind of program we just heard about?

DR. MAHER: Dr. Sanchez spoke wonderfully to potential barriers that exist. The key is getting the guidelines set up, getting a guideline and then a standard reference system that we can use. I think education is key in all of this, in getting everyone on board, educating clinicians, educating nurses, educating the hospital staff, administration staff, educating

insurance companies. Educating our patients is going to be so important.

The other thing I think that will be important as a potential barrier to change would be cost. What does the cost look like for implementing universal screening? What does the cost look like to the patients?

Then getting the standardization of nanomoles per liter going forward.

DR. GUYTON: Right. Let's finish by asking each of you to describe one or more points that you think are most important. Let me just inject here that the National Lipid Association came out with a Scientific Statement on lipoprotein(a) published in the Journal of Clinical Lipidology in 2019.

DR. TOKGÖZOĞLU: I think Lp(a) is an independent and causal risk factor, which is usually underdiagnosed, not known well enough, and not taken into consideration in general cardiology practice. We certainly need unified standardized approaches to measurement of Lp(a), so that the clinicians can base their decisions on it. I'm hoping to see some significant therapies in the future to treat this, which will make a big impact because Lp(a) is high in more than 20% of the population. In addition to the medical organizations, I think patient organizations also have a role to increase awareness. We certainly need to increase awareness not only in the medical community, but in the patient community as well.

DR. GUYTON: Great. Dr. Sanchez.

DR. SANCHEZ: It is important for our individual organizations to speak on lipoprotein(a) not in a cacophony of discordant solo voices but to sing as one chorus with harmonized voices about Lp(a). This will eliminate confusion among clinicians and patients. I think unifying around measurement, continuing to gather data and bring even more clarity to the epidemiology of Lp(a) and its consequences, and then moving towards identifying those therapeutic opportunities to lower risk and save lives are important steps forward.

DR. GUYTON: Thank you. Dr. Maher.

DR. MAHER: I'm looking forward, as the research continues, to learning more about Lp(a) and learning more about these emerging therapies. I'm very excited for the future for patients who are participating in these trials and patients who will get these therapies in the future. In general I'm very hopeful and very excited about how the future looks towards Lp(a). We need to continue to focus on the standardization and guidelines in going forward.

DR. GUYTON: Great. And Dr. Underberg.

DR. UNDERBERG: I wear two hats. I'm a lipidologist. I see patients referred for lipid disorders. But I'm also an internist, and I spend part of my time doing primary care and spend a lot of time educating colleagues in primary care. I actually think that a major role for us right now is to translate this actional information for our colleagues. All too often when I make a recommendation about screening Lp(a), the response I hear is, "There's nothing you can do about it, so why check it?" Obviously as we've discussed today, that's clearly not the case.

Even before we have new therapeutic options available to us, identifying the importance of risk in patients is a key factor for education, whether it's physicians, nurse practitioners, physician assistants, or whomever is providing primary care for the patient. I think that's one of the most important things we can do. If we don't identify patients and families with high Lp(a), there's not much we can do about addressing their risk.

DR. GUYTON: I hope that this discussion can have an impact on everyone who reads it. I think back to that day in 1980 when Gösta Dahlén walked into his new laboratory in Houston, having traveled from the city of Boden near the Arctic Circle in Sweden. How much we owe to Doctors Berg, Dahlén, Utermann, and all who have contributed thus far, and to you and many colleagues who continue to help us learn about a major cardiovascular risk factor. Thank you.