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Global think tank on the clinical considerations and management of lipoprotein(a): The top questions and answers regarding what clinicians need to know

Salim S. Virani
Baylor College of Medicine, United States, salim.virani@aku.edu

Marlys L. Koschinsky
Schulich School of Medicine and Dentistry, Canada

Lisa Maher
Cedar Valley Cardiovascular Center, United States

Anurag Mehta
Emory University School of Medicine, United States

Carl E. Orringer
University of Miami Miller School of Medicine, United States

See next page for additional authors

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Global think tank on the clinical considerations and management of lipoprotein(a): The top questions and answers regarding what clinicians need to know

Salim S. Virani [a], Marlys L. Koschinsky [b], Lisa Maher [c], Anurag Mehta [d], Carl E. Orringer [e], Raul D. Santos [f,g], Michael D. Shapiro [h], Joseph J. Saseen [i,*]

[a] Section of Cardiovascular Research, Baylor College of Medicine & Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, USA
[b] Robarts Research Institute, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada
[c] Cedar Valley Cardiovascular Center, Waterloo, Iowa, USA
[d] Emory University School of Medicine, Atlanta, GA, USA
[e] University of Miami Miller School of Medicine, Miami, FL, USA
[f] Heart Institute (InCor) University of Sao Paulo, Sao Paulo, Brazil
[g] Hospital Israelita Albert Einstein, Sao Paulo, Brazil
[h] Wake Forest University School of Medicine, Center for Prevention of Cardiovascular Disease, Winston-Salem, NC, USA
[i] University of Colorado Anschutz Medical Campus, Aurora, CO, USA

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ABSTRACT

Evidence from Mendelian randomization studies suggest that lipoprotein(a) (Lp(a)) has a causal role in the development of atherosclerotic cardiovascular disease risk. However, guidelines and consensus statement recommendations vary regarding how clinicians should incorporate Lp(a) into patient care. To provide practical answers to key questions pertaining to Lp(a) that clinicians will find useful when assessing and treating patients, a global think tank was convened. Representatives from seven national and international stakeholder organizations answered questions that were focused on: Lp(a) measurement; ethnic, gender, and age considerations; factoring Lp(a) into risk assessment; and current and emerging treatment options for elevated Lp(a). This manuscript summarizes the finding from this global think tank. Areas requiring further investigation were identified, and the need to standardize reporting of Lp(a) levels to ensure harmonization and comparability across laboratories and research studies is emphasized.

Contents

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; AVS, aortic valve stenosis; CAC, coronary artery calcification; CHD, coronary heart disease; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; FH, familial hypercholesterolemia; HRT, hormone replacement therapy; IL6, interleukin-6; IFCC, International Federation of Clinical Chemistry; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); Lp(a)-C, cholesterol associated with the LDL-like component of Lp(a); MACE, major adverse cardiovascular events; NLA, National Lipid Association; OxPL-apoB, oxidized phospholipids on apoB; ODYSSEY, acute coronary syndrome during treatment with alirocumab; PCSK9, proprotein convertase subtilisin/kexin type 9; SCORE, systematic coronary risk estimation; siRNA, small interfering RNA; WHO, World Health Organization.

* Corresponding author at: University of Colorado Anschutz Medical Campus, 12850 E. Montview Blvd. (c238), Aurora, Colorado 80045, USA.
E-mail address: Joseph.Saseen@CUAnschutz.edu (J.J. Saseen).

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Introduction

Lipoprotein(a) (Lp(a)) is a low-density lipoprotein (LDL)-like particle with an additional protein apolipoprotein(a) [Apo(a)] coiled around it.[1] Kåre Berg discovered Lp(a) in human serum in 1963 during a study of variation in LDL antigenicity.[2] Recent Mendelian randomization studies point towards a possible causal role of Lp(a) in atherosclerotic cardiovascular disease (CVD;ASCVD) risk. Data from 460,506 middle-aged participants in the United Kingdom Biobank demonstrated that Lp(a) predicts incident ASCVD among both primary and secondary CVD prevention patients, with an increase in risk demonstrated with increasing Lp(a) concentrations.[3] Despite the known relationship between Lp(a) and ASCVD risk, there are several questions related to the full deployment of this risk marker in the global context of patient care.

In 2019, the National Lipid Association (NLA) published a Scientific Statement regarding the use of Lp(a) in clinical practice with several recommendations.[4] However, other organizations have also published expert recommendations with several similarities and differences.[5–7] To facilitate a harmonized approach to Lp(a), the NLA convened a Global Think Tank of seven stakeholder organizations in 2020 with the objective to deliver a globally accepted expert consensus on the measurement and management of Lp(a) in clinical practice. The stakeholder organizations including the Association of Black Cardiologists, American College of Cardiology, American Heart Association, European Atherosclerosis Society, International Atherosclerosis Society, National Institutes of Health, and Preventive Cardiovascular Nurses Association, collaborated with the NLA to design the concept of the Think Tank and to complete this initiative.

The Global Think Tank on the Clinical Considerations and Management of Lp(a) was conducted as a half-day meeting on November 30, 2020. There were 21 participants: five planning committee members appointed by the NLA, one representative appointed by each stakeholder organization, two fellows-in-training, and seven additional special guests appointed to assure broad scientific and clinical expertise. Focused questions, informed by a survey of the stakeholders, were identified as the top issues that clinicians have about Lp(a) and were answered during the Think Tank meeting:

1) How should Lp(a) be measured?
2) What are the ethnic, gender, and age considerations while considering Lp(a) associated ASCVD risk?
3) How should Lp(a) be factored into risk assessment?
4) What are the current and emerging treatment options for elevated Lp(a)?
5) What further research is needed?

This manuscript summarizes the discussion of the Think Tank meeting in response to these questions and is not considered a guideline. The aim of this review is to provide succinct summary of recommendations for practicing clinicians pertaining to each of the 5 questions.

How should Lp(a) be measured?

Challenges and solutions for Lp(a) measurement

Issues in the measurement of Lp(a) have created roadblocks for the standardization and harmonization of commercial assays. This has hindered comparison of data from studies using different methods of Lp(a) measurement and created uncertainty for clinicians regarding interpretation of clinical Lp(a) measurements.[8] As such, reliable methodologies for measuring Lp(a) that address both standardization and harmonization are needed.

The structure of Lp(a) creates unique challenges for its measurement compared to other lipoproteins. In addition to its LDL-like moiety, Lp(a) also contains the unique apolipoprotein(a) (apo(a)) component. Apo(a) consists of 11 types of kringle sequences, ten of which (designated apo(a) KIV type 1 – apo(a) KIV type 10) are highly similar to plasminogen kringle 4. The apo(a) KIV type 2 sequence itself is present in a variable number of repeated copies (ranging in number from 3 to >40), giving rise to plasma Lp(a) isoform size heterogeneity (Fig. 1). Of note, there is a well-established general inverse relationship between the isoform size of Lp(a) and its levels in plasma, with smaller isoforms associated with higher plasma Lp(a) concentrations.[9] Although differences in isoform size predominantly determines plasma levels of Lp(a), it does not entirely explain the differences in levels across ethnic groups.[10] Other influences e.g. single nucleotide polymorphisms, two splice site variants in the K-IV type-2, and other unknown mechanisms also play a role.

The presence of the repeated kringle IV type 2 sequence in apo(a) creates many of the Lp(a) measurement challenges. Expressing Lp(a) as a mass concentration (milligrams/deciliter; mg/dL) introduces an inherent bias because a given mass of Lp(a) represents a lesser number of particles for large isoforms and a greater number of particles for small isoforms. Moreover, converting from mass concentrations to particle concentrations using a single conversion factor of 2.5 will overestimate the concentration of larger isoforms and underestimate the concentration for smaller isoforms (Fig. 2). To manage this challenge, measurement of Lp(a) using particle concentration units (nanomoles/l; nmol/L) is becoming increasingly common.[4] Many platforms using high throughput measurement methods (immunoturbidometric or immunonephelometric methods) now report Lp(a) measurements in nmol/L. To ensure optimal minimization of isoform size bias in Lp(a) measurement, a number of commercial assays include five different isoform sizes of Lp(a) as calibrators, each of which have been standardized against the World Health Organization/International Federation of Clinical Chemistry and Laboratory Medicine (WHO/IFCC) reference material that is reported in nmol/L units.

The mass spectrometry-based approach for Lp(a) measurement is an exciting new development.[11] Unique peptide fragments of apo(a), not present in the repeated KIV2 domain, can be specifically detected and their concentration assessed against an appropriate internal standard with this approach. This approach is suited for high throughput

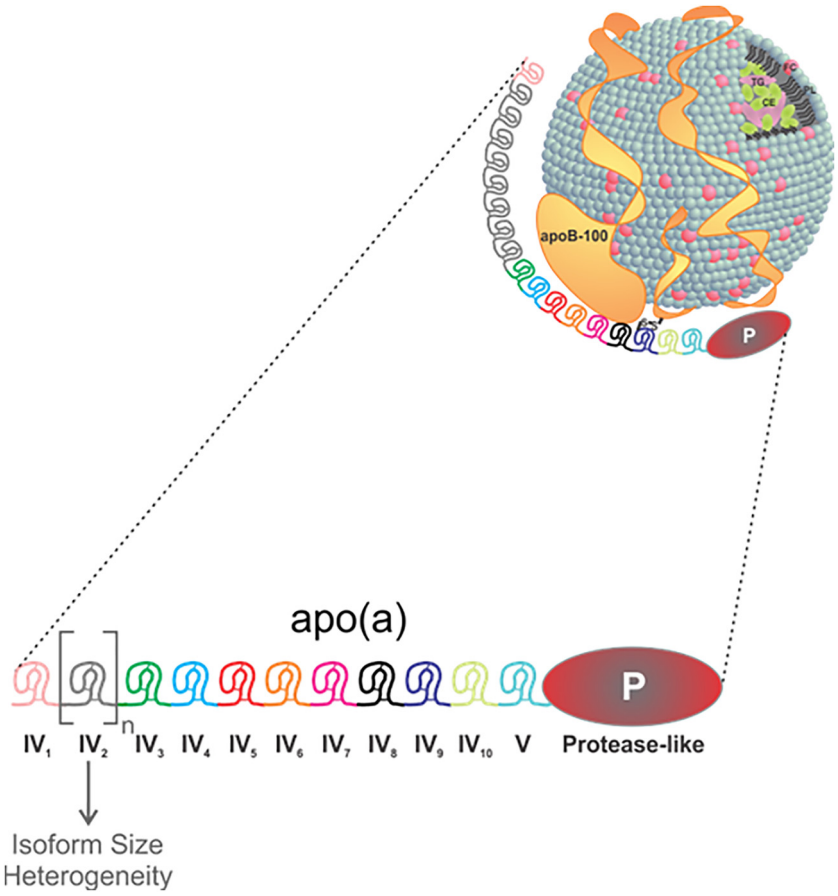

Fig. 1. Structure of Lp(a) and apo(a). Lp(a) consists of apo(a) covalently linked to an apoB100-containing lipoprotein moiety consisting of a core of cholesteryl esters (CE) and triacylglycerols (TG) surrounded by a shell of phospholipids (PL) and free cholesterol (FC). Apo(a) contains 10 types of kringle IV (KIV) repeats, one of which (KIV2) is present in different numbers in different isoforms, as well as a kringle V domain (KV) and an inactive protease-like domain (P).

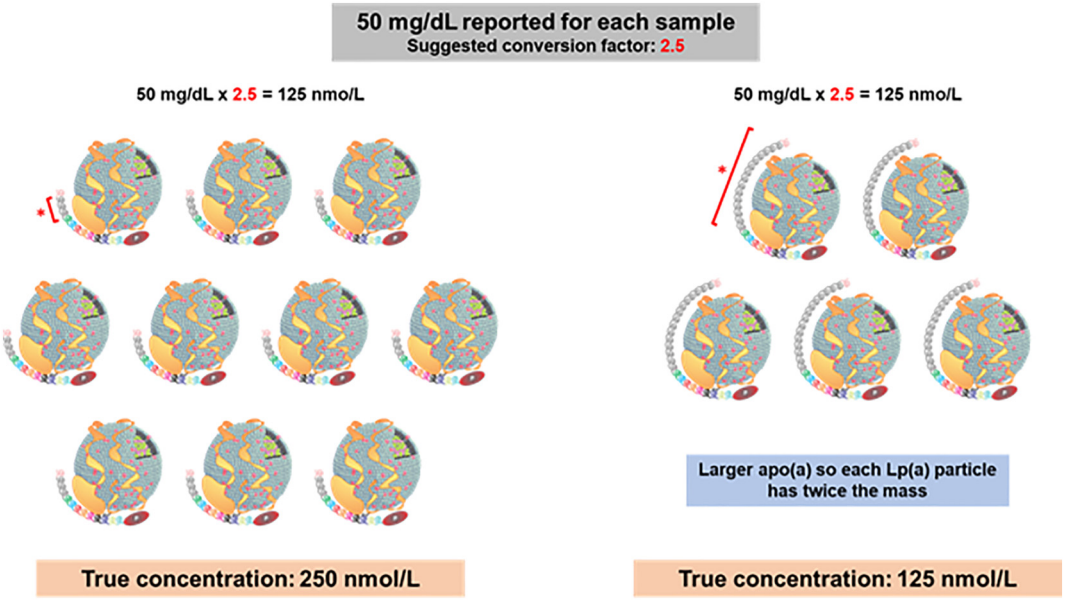

Fig. 2. Relationship between mass and particle concentrations of Lp(a) species containing differently sized apo(a) isoforms. For a given mass of particles, there will be more particles when the mass of each particle is smaller. Assays measuring in mg/dL would register the concentrations of each of these groups of particles as the same; however, there are twice as many of the small particles, as reflected in the nmol/L concentrations. The asterisked square brackets (red) denote the size polymorphic region in apo(a) that accounts for the difference in molecular mass between small and large Lp(a) isoforms.

applications and addresses issues of isoform size bias that are often encountered in immunochemical assays as discussed above.

Accurate measurement of Lp(a) is of increasing importance as the field moves toward considering Lp(a) as a component of clinical risk assessment and as specific Lp(a)-lowering therapies become available.[3] Lp(a) levels are established in early childhood and remain relatively stable throughout an individuals' life and as such a single measurement is generally considered sufficient. However, several conditions can affect Lp(a) levels. For example, transient elevations of Lp(a) immediately following a CVD event have been reported. It has also been well-established that Lp(a) levels increase post-menopause although, the significance of this elevation is not well known. Additionally, a variety of disease states may modulate Lp(a) levels including liver disease, chronic kidney disease, and diabetes mellitus. In these cases, additional Lp(a) measurements may be necessary. Transient increases in Lp(a) levels have been reported in acute inflammation[12]; this occurs primarily due to an interleukin-6 (IL-6) response element in the *LPA* gene that upregulates its expression.[13] As such, baseline Lp(a) levels cannot be reliably determined during the acute phase of inflammation.

The cholesterol associated with the LDL-like component of Lp(a) (Lp(a)-C) is included in clinical measurements of LDL-C. A value of 30% has been proposed as a "correction" factor for Lp(a)-C[14] but since the amount of cholesterol in the Lp(a) particle may vary significantly, this approach is not currently recommended for widespread clinical use.[14]

What are the ethnic, gender, and age considerations for Lp(a) risk?

Race/ethnicity

There are distinct differences in Lp(a) levels, apo(a) isoform size distribution, and *LPA* single nucleotide polymorphisms across racial and ethnic groups. Black ancestry is associated with the highest Lp(a) levels and the distribution of Lp(a) levels in this population is more normal than the typical skewed distribution seen in other racial and ethnic groups. Relative to Blacks, South Asians have the second highest median Lp(a) level, and this is followed by Whites, Hispanics, and East Asians.[10,15–17] Nonetheless, it is clear that elevated Lp(a) is independently associated with ASCVD in all racial and ethnic groups that have been evaluated.[10,18–21] One analysis from the Atherosclerosis Risk In Communities study demonstrated that Lp(a) concentration was similarly associated with ASCVD risk in both Blacks and Whites.[22] However, different racial and ethnic groups have distinct risk factor profiles that could influence the contribution of Lp(a) to ASCVD risk. Finally, differences in levels across ethnic groups could also contribute to differences in population attributable risk of CVD associated with Lp(a).

It is unlikely that there are unique differences in the fundamental pathophysiology of Lp(a) in various ethnic groups. Therefore, a universal Lp(a) threshold for increased risk has been proposed by the NLA.[4] Data from the U.K. Biobank, the largest prospective cohort with Lp(a) data for both Black and South Asian individuals, has provided insight regarding median Lp(a) concentrations among different race groups.[3] Significant differences in median Lp(a) concentrations were observed across race/ethnicity (16,19, 31, and 75 nmol/L in Chinese, White, South Asian, and Black individuals, respectively). However, analysis of various racial subgroups yielded similar estimates of ASCVD risk which appeared to be linear and irrespective of whether a uniform or race-specific percentile threshold for elevated Lp(a) level was used.

Sex

There are notable sex differences in plasma Lp(a) concentrations. Lp(a) levels remain relatively constant throughout life in men, and tend to increase with age in females after menopause.[23] An analysis from the Heart and Estrogen/progestin Replacement Study demonstrated that elevated Lp(a) levels were independently associated with an increased risk for coronary heart disease (CHD) in post-menopausal females.[24] Moreover, combination hormone replacement therapy (HRT) lowered Lp(a) by approximately 15–20%. Nonetheless, given the association between HRT and risk of ASCVD, use of HRT to lower Lp(a) in perimenopausal/postmenopausal females is not recommended.[4]

Age

Universal screening of Lp(a) in children is controversial. Lp(a) levels are established early in childhood and remain relatively constant throughout life.[4] Available evidence suggests a significantly increased risk of incident childhood-onset ischemic stroke related to elevated Lp(a).[25] Lp(a)-related stroke in children is rare and appears to be non-atherosclerotic in nature, given the time necessary for atherosclerosis to develop and events to occur. More commonly, lifelong elevation of Lp(a) is associated with ASCVD, including stroke. Individuals with extremely elevated Lp(a) (>180 mg/dL) have been proposed to demonstrate a similar ASCVD lifetime risk as those with heterozygous familial hypercholesterolemia.[26] On this basis, some experts suggest universal Lp(a) screening of all children, though there is not a uniform agreement with this suggestion. Universal Lp(a) screening might allow for initiation and emphasis of healthy lifestyle at a young age and may facilitate meticulous screening and management of traditional ASCVD risk factors over the life course. While universal screening remains controversial, there is general agreement that cascade Lp(a) screening of children is reasonable when a parent with elevated Lp(a) is identified, particularly when there is a family history of premature ASCVD.[4] Moreover, when a child is the index case, reverse cascade screening of the parents is recommended.

How should Lp(a) be factored into ASCVD risk assessment?

The relationship between Lp(a) and ASCVD risk has been well established in epidemiological studies and meta-analyses,[3,27–29] Mendelian randomization studies,[30,31] and genome-wide association studies.[15,32] The UK Biobank has demonstrated substantial racial diversity in relation to median Lp(a) concentrations.[3] Despite these differences, risk for incident ASCVD over a median follow-up of 11.2 years was similar and showed a linear gradient regardless of ethnicity, with a 50 nmol/L increase in Lp(a) being associated with hazard ratios of 1.11, 1.10, and 1.07 for White, South Asian, and Black individuals, respectively. Using race-specific 90th percentile values (White: ≥168.2 nmol/L, South Asian: ≥139.5 nmol/L, and Black ≥211.7 nmol/L), and employing Cox proportional hazards regression models with covariates of enrollment age, and sex, the hazard ratios for incident ASCVD comparing those above versus below the 90th percentile were 1.52 (95% CI 1.46–1.59), 1.35 (95% CI 1.30–1.78) and 1.51 (95% 1.05–2.18) for Whites, South Asians, and Blacks respectively. Furthermore, inclusion of Lp(a) measurement in addition to models adjusted for Framingham Risk Scores and Reynolds Risk Scores in a cohort of 826 participants in the Bruneck study followed for 15 years for cardiovascular disease events resulted in either upward or downward net reclassification improvement of 39.6% in those originally classified as being at intermediate ASCVD risk.[33]

Variable and ethnicity-specific associations between elevated plasma Lp(a) levels, oxidized phospholipids on apoB (OxPL-apoB), Lp(a) genetic markers and major adverse cardiovascular events (MACE) was demonstrated in a study of 1792 Black, 1030 White, and 597 Hispanic enrollees in the Dallas Heart Study. In this study *LPA* SNPs, apo(a) isoforms, Lp(a), and OxPL-apoB levels were studied and ASCVD outcomes assessed over a median 9.5 years of follow-up. Despite the presence of ethnicity-specific differences in *LPA* genetic markers, the relationship of Lp(a) to MACE was best explained by elevated plasma Lp(a) or OxPL-apoB levels.[34]

The relationship between high Lp(a) concentrations and increased ASCVD risk has been demonstrated in studies of high-risk primary and secondary CVD prevention populations with high levels of LDL-C,[35,36]

and in those achieving LDL-C < 70 mg/dL.[37,38] In addition, a patient level meta-analysis of seven randomized, placebo-controlled, statin outcome studies was used to calculate hazard ratios (HRs) for fatal or non-fatal CHD, stroke, or revascularization procedures across predefined Lp(a) groups (15 to <30 mg/dL, 30 to <50 mg/dL, and >/=50 mg/dL, vs <15 mg/dL), before pooling estimates using multivariate random-effects meta-analysis. This study demonstrated that elevated baseline and on-statin Lp(a) concentrations showed an independent and approximately linear relation with CVD risk.[39]

Evidence supports a causal association between elevated Lp(a) and calcific AS.[40] The association between elevated Lp(a) levels and incident calcific aortic valve stenosis (AVS) was demonstrated in a study of 17,553 participants of the European Prospective Investigation into Cancer -Norfolk study, among whom 118 developed AVS during a mean follow-up of 11.7 years. The rs10455872 genetic variant in *LPA* was genotyped in 14,735 study participants, who simultaneously had Lp(a) measurements, and in another study of 379 individuals with echocardiographically-confirmed AVS and 404 controls. The study showed that those with high Lp(a) levels have an increased risk for AVS and that the rs10455872 variant, which is associated with higher Lp(a) levels, is also associated with increased risk of AVS, suggesting possible causality of this variant.[41]

A subsequent study was designed to determine whether levels of Lp(a) and oxidized phospholipids were associated with aortic stenosis progression and CVD death. A total of 220 patients with mild to moderate AVS were studied with a primary endpoint of progression rate of AS, measured by the annualized increase in peak aortic jet velocity in m/s/year by Doppler echocardiography. The secondary endpoint of the study was the composite of aortic valve replacement or cardiac death. Over 3.5 ± 1.2 years of follow-up and after adjustment for age, sex and baseline aortic stenosis severity, aortic stenosis progression was found to be more rapid and requirement for aortic valve replacement greater for those in the top tertile of Lp(a) concentrations [Lp(a) (>58.5 mg/dL) and OxPL-apoB (>5.50 nmol/L)] versus the middle and bottom tertiles [Lp[a] ≤ 58.5 mg/dL and OxPL-apoB ≤5.50 nmol/L].[42]

Table 1 reviews guideline-recommended use of Lp(a) for risk assessment and demonstrates that there is substantial divergence of perspective among guidelines on how the clinician should most appropriately use Lp(a) for risk assessment in clinical practice. The AHA/ACC/multisociety Cholesterol Guideline[5] uses an elevated Lp(a) value as a risk enhancing factor among those at borderline or intermediate 10-year ASCVD risk, but only if measured at the clinician's discretion. The European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Dyslipidemia Guidelines[6] suggest that Lp(a) measurement should be *considered* at least once in each person's lifetime, with the primary objective to determine whether, based on a value of ≥180 mg/dL or 430 nmol/L, there is a presence of a risk equivalent state to familial hypercholesterolemia. They also use elevated Lp(a), but with values lower than those above, to aid in risk reclassification and treatment decision-making in those presumed to be at moderate risk using

Table 1
Guideline-recommended use of lipoprotein(a) for risk assessment.

Guideline	Whom to Screen	How is it used	Values used for decision-making	Comments
2018 American Heart Association/American College of Cardiology/-Multisociety Guideline[5]	No recommendations	If measured, as a risk enhancing factor in addition to the Pooled Cohort Equations in adults 40–75 years of age	50 mg/dL or 125 nmol/L	1. Used only as aid in statin initiation decision-making for primary prevention
2019 European Society of Cardiology/ European Atherosclerosis Society[6]	Screen at least once during lifetime	To identify those at increased ASCVD risk in primary prevention	180 mg/dL or 430 nmol/L confers lifetime risk as high as heterozygous FH "Less extreme elevations" to aid in treatment intensity decision-making in those between moderate- and high-risk using SCORE risk assessment	1. No specific definition of "less extreme elevation" of Lp(a)
National Lipid Association 2019[4]	Selectively screen for primary or secondary prevention	To identify those at risk for initial ASCVD event or to identify those at risk for recurrent or progressive ASCVD or valvular aortic stenosis	50 mg/dL or 100 nmol/L in Caucasians or > 150 nmol/L in Blacks Is reasonable to refine risk assessment in: 1. 1st degree relatives of those with premature ASCVD 2. Personal history of premature ASCVD 3. Those with severe primary hypercholesterolemia or FH suspects May be reasonable: 1. To inform risk discussion in adults with 5–7.4% 10-yr ASCVD risk 2. To identify cause of less than anticipated LDL-C lowering with a statin 3. For cascade screening of those with LDL-C ≥ 190 mg/dL 4. To identify those at risk for progressive valvular aortic stenosis	1. Emphasized ethnic differences in Lp(a) levels 2.Extended recommendations to secondary prevention 3. First guideline to recommend consideration as marker for progressive valvular aortic stenosis
2021 Canadian Cardiovascular Society Guidelines[7]	Screen once during lifetime as part of initial lipid screening	For elevated values: To inform intensity of behavioral and drug therapy decision-making for primary and secondary prevention	50 mg/dL or 100 nmol/L Primary prevention: 1. More intensive behavior modification and management of other ASCVD risk factors 2. Consider CAC scoring 3. Consider earlier introduction of statins or other lipid lowering therapy, esp. in intermediate and/or low-risk individuals with LDL-C 135–193 mg/dL Secondary prevention: 1. Intensify LDL-C lowering therapy 2. Consider PCSK9 inhibitors, especially in post ACS patients	1. First major society guideline to recommend universal screening and Lp(a) measurement in treatment decision making in primary and secondary prevention

systematic coronary risk estimation (SCORE) risk assessment. The NLA Lp(a) Scientific Statement[4] supports selective screening of Lp(a) to be used in treatment decision-making for both primary and secondary ASCVD prevention and in those with valvular aortic stenosis. The Canadian Cardiovascular Society Dyslipidemia Guidelines[7] provides the strongest recommendation favoring Lp(a) screening, indicating that it *should be measured* once during lifetime as part of initial lipid screening and be used in treatment decision-making both for primary and secondary ASCVD prevention. It is most likely that the basis for these differing recommendations emanates from a variety of factors, including:

- Different Lp(a) measurement techniques employed in the literature across studies and their differential impact on various ethnic groups given differences in Lp(a) isoform size across ethnicities
- Differences in Lp(a) reporting (mg/dL vs. nmol/L) in clinical practice
- Lack of clinical trial data supporting Lp(a) as a treatment target
- Lack of currently available treatments that have been convincingly demonstrated to lower ASCVD or aortic stenosis risk in those with elevated Lp(a) in the absence of lowering other atherogenic lipoproteins

If the clinician decides to measure Lp(a) in clinical practice, what values should be used as indicators of significantly increased risk?

- A value of ≥180 mg/dL or 430 nmol/L may indicate the need for aggressive LDL-C lowering and attention to addressing other non-lipid modifiable risk factors.[6]
- Although there has been a suggestion that a reasonable "cut point" for an "elevated Lp(a) is ≥100 nmol/L in Whites and probably Hispanic/Latinos and ≥ 150 nmol/L in Blacks,[4] these values represent approximations and the clinician must recognize that Lp(a)-related risk is a continuum, with no specific "cutpoint".[3]
- Lp(a)-related risk, like that of other risk factors, is of greatest clinical significance in those with additional ASCVD risk factors.

In view of the above considerations, it appears reasonable at this time for the clinician to adopt a perspective for clinical use of Lp (a) that employs the following approach:

1. Obtain Lp(a) values only if it is likely that the results will impact clinical decision making.
2. Obtain Lp(a) values in the absence of acute illness, as Lp(a) levels may be elevated as an acute phase reactant.
3. Avoid serial Lp(a) measurement, as values are relatively stable throughout one's lifetime
4. If one takes the perspective that Lp(a) does not need to be measured in all individuals, reasonable candidates for Lp(a) measurement, as an indicator for the potential for more aggressive preventive treatment strategies includes those patients with:
   - o Heterozygous familial hypercholesterolemia (FH)
   - o Premature ASCVD
   - o Family history of premature ASCVD
   - o Progressive ASCVD despite optimal medical therapy
   - o Recent acute coronary syndromes[43]
   - o Family history of elevated Lp(a)

What are current and emerging treatment options for elevated Lp (a)?

Despite strong association between elevated Lp(a) concentrations and ASCVD and aortic valve disease risk as discussed above, there is lack of robust evidence which demonstrated that reducing Lp(a) levels reduces clinical ASCVD events.[4,44,45] Table 2 shows the impact of various therapies on plasma Lp(a) concentrations and the possible impact on ASCVD.

Table 2
Lipid modifying therapies, their impact on lipoprotein(a) plasma concentrations and ASCVD.

Therapy	Impact on Lp (a) plasma concentration	Impact on ASCVD
Statins[39]	Neutral or slight increase	Robust due to LDL-C reduction[5]
PCSK9 inhibitors[50]	20–25% reduction	Robust due to LDL-C reduction[5]; impact of Lp(a) reduction possible in subgroup analyses[55,57]
Ezetimibe[63]	Neutral	Moderate due to LDL-C reduction[5]
Niacin[59]	20–38% reduction	Impact of Lp(a) reduction on events negligible[37,64]
Apolipoprotein B antisense oligonucleotide (mipomersen)[60]	26% reduction	Possible due to LDL-C lowering,[65] impact of Lp(a) reduction unknown
Apolipoprotein(a) antisense oligonucleotide (pelacarsen)[61]	Up to 80% reduction	Currently unknown
Lipoprotein apheresis[58,59]	19–88% reduction	Possible[44]

In the presence of elevated Lp(a) concentrations, treatment for both primary and secondary ASCVD prevention should focus on optimal control of modifiable risk factors.[4,45] Education directed at smoking cessation, nutrition, and physical activity should be provided to all patients. There is controversy as to whether clinicians should reduce LDL-C, prescribe antiplatelet therapy, or prescribe PCSK9 inhibitors for either LDL-C or Lp(a) lowering in primary and secondary ASCVD prevention patients with elevated Lp(a).

Primary prevention

For primary prevention patients with high Lp(a) levels, it is essential to perform a thorough risk assessment which includes the following key elements: assessment of individual risk factors, calculation of ASCVD risk, and assessment of family history of early onset ASCVD. This should be used to direct education and treatment. If the calculated 10-year risk of ASCVD is borderline (5.0 to 7.4%) or intermediate risk (7.5–19.9%), or if there is family history of early ASCVD or familial hypercholesterolemia, elevated Lp(a) should be considered a risk enhancing factor favoring more aggressive LDL-C lowering therapy.[4,5,46]

Despite optimal control of risk factors, subclinical atherosclerosis might be present in primary prevention patients.[47] Coronary artery calcification (CAC) measurement can provide further insight that favors aggressive LDL-C lowering therapy in borderline and intermediate risk patients (e.g., CAC scores ≥100 Agatston units or ≥ the 75th percentile for age and sex in young individuals).[5] The opposite may be also true with a CAC score of zero, where statin therapy may be deferred among borderline and intermediate risk patients.[48–50] Imaging may help to stratify risk in individuals with elevated Lp(a) and absence of subclinical coronary atherosclerosis as suggested by an analysis from the Multi Ethnic Atherosclerosis Study.[51] One should start statin therapy for LDL-C reduction aimed at delaying or reversing the progression of the disease.[52] It is debatable whether LDL-C lowering is needed in people with high Lp(a) and low estimated ASCVD risk, especially in the absence of family history of early ASCVD, or in those with a CAC score of zero.

The use of low-dose aspirin versus placebo was investigated in the Women's Health Study.[53] Carriers of a rare *LPA* gene variant (rs3798220) that is associated with elevated Lp(a) concentrations and small apo(a) isoform sizes (present in 3.7% of the population) had a 2-fold higher ASCVD risk. Interestingly, a relative 56% reduction in ASCVD risk was observed in carriers on aspirin therapy versus non-carriers. This may reflect aspirin's antithrombotic effect against enhanced prothrombotic properties of the apo(a) protein. Despite this,

there is no robust evidence from large, randomized trials to confirm that antiplatelet therapies are beneficial for patients with elevated Lp(a) especially when LDL-C is lowered by pharmacological therapy.[54]

Statin therapy may increase Lp(a) levels as seen in the meta-analysis by Tsimikas, et al., which analyzed data from six randomized clinical trials.[43] This meta-analysis found a mean percentage change in Lp(a) (8.5 to 19.6%) compared to the placebo group (0.4–2.3%). However, in the meta-analysis by Willeit et al., with individual data of 29,000 individuals enrolled in statin trials, there was a pooled −0·4% (95% CI −7 to 7) change in Lp(a).[39] Still, there was heterogeneity among these trials with 3 showing a mean increase (between 2% and 15%) and 4 showing, a mean decrease (between −1% and −13%) in Lp(a) levels. The question remains whether this possible statin induced Lp(a) increase is clinically relevant. In analyses from the JUPITER trial, the median change in Lp(a) levels was zero among those randomized to rosuvastatin or placebo although, there was a small but statistically significant positive shift in the overall Lp(a) distribution among those on rosuvastatin.[38] Both baseline and on-treatment Lp(a) levels were associated with residual ASCVD risk independent of LDL-C and other factors. Rosuvastatin reduced the risk of cardiovascular events to a similar degree without any heterogeneity of effect among those with Lp(a) levels above or below the median. While reduction in LDL-C remains the current standard of care, clinicians should evaluate the residual cardiovascular risk to individualize patient treatment.

Secondary prevention

In individuals with ASCVD, there is evidence that even with the use of statin and antiplatelet therapies, the residual risk of ASCVD is increased by high Lp(a).[5,39,56] Management of individuals with elevated Lp(a) should focus on intensifying LDL-C lowering and addressing other modifiable risk factors.[56,57] The higher risk of events in those with high Lp(a) was associated with a greater absolute benefit of further LDL-C lowering with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.[56,57]

Whether Lp(a) lowering by PCSK9 inhibitors (around 20–25%)[50] brings additional benefit in terms of ASCVD risk reduction is a matter of debate. Two additional analyses of the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY) trial suggest that modification of Lp(a) burden by alirocumab (in patients receiving statin therapy), reduced the risk for a cardiovascular event independent of concurrent reduction in LDL-C.[55,57] Currently, PCSK9 inhibitors are not indicated to lower Lp(a) and should not be used for this specific purpose.

Lipoprotein apheresis affects multiple lipoproteins; there are minimal data regarding the effect of specific removal of Lp(a) alone. However, one observational study suggests that during a 5-year follow-up, a 70% reduction in Lp(a) with lipoprotein apheresis was associated with a reduced risk of ASCVD event rates when compared with ASCVD event rates for the two years before the start of regular apheresis therapy.[44]

It is unclear how intensive Lp(a) lowering should be to prevent ASCVD events.[56] Two Mendelian randomization analyses indicate that the risk of CHD is reduced by Lp(a) lowering. Although both studies suggest reduction in CHD, the extent of Lp(a) lowering needed to reduce CHD were substantially different from each other. One study suggested that an absolute reduction in Lp(a) by approximately 100 mg/dL is needed to reduce CHD risk similarly to reduction of LDL-C by 1 mmol/L or 38.67 mg/dL.[26] However, another study estimated that Lp(a) lowering of 65.7 mg/dL is needed to reach the same effect as a 38.67 mg/dL lowering of LDL-C.[58]

Both niacin and the antisense oligonucleotide against apolipoprotein B mipomersen may reduce Lp(a) by a mean of 20–38% and 26%, respectively.[59,60] However, there is no evidence that this reduction in Lp(a) leads to a reduced risk of ASCVD events. Therefore, these drugs are not recommended for patients with elevated Lp(a).

The Lp(a) HORIZON trial (NCT04023552) is an ongoing outcomes study to assess the efficacy and safety of an antisense oligonucleotide targeting *LPA* mRNA that robustly reduces apolipoprotein(a) synthesis (pelacarsen 80 mg).[61] Pelacarsen in this trial will be given by subcutaneous injection once monthly to participants with established CHD and one of two Lp(a) strata (>70 mg/dL and > 90 mg/dL). Hopefully the results will provide evidence to show a clear benefit from Lp(a) lowering independent of other lipid parameters in secondary ASCVD prevention settings. Lastly, small interfering RNA (SiRNA) are also being studied currently to assess their role in Lp(a) lowering.[62]

Further research needs

Although our knowledge of Lp(a) continues to grow, there are several important questions that remain unanswered:

1. How should reporting of Lp(a) (mass concentration, particle concentration) in clinical and research domains be standardized?
2. Should universal screening be performed to identify those with elevated Lp(a) levels?
   a. Which particular groups of patients should routinely receive screening for elevated Lp(a) levels?
   b. Should cascade screening be systematically performed in relatives of people with high Lp(a)?
3. Should a threshold Lp(a) level be used to identify those at higher risk of ASCVD events? Is the threshold level different when assessing risk of calcific aortic stenosis? Is the risk threshold the same for similar level of Lp(a) elevation across various racial and ethnic groups? Is the risk threshold the same for those on statin therapy? Is the risk threshold the same for primary and secondary prevention patients? What is the impact of correcting LDL-C levels for Lp(a) cholesterol both from a risk assessment and therapeutic perspective?
4. How should Lp(a) be incorporated in ASCVD risk calculators?
5. Does lowering of Lp(a) without altering the levels of other lipoproteins reduce risk of ASCVD events and calcific AVS?
6. Given the post-menopausal rise in Lp(a), should females be screened for elevated Lp(a) at or after menopause?
7. Should all children have Lp(a) measured at the time they undergo universal lipid screening (between the ages 9–11)?
8. How much reduction in Lp(a) is necessary to prevent ASCVD events?
9. Is it safe to reduce high Lp(a) levels?

Conclusions

In this manuscript, we summarize practical answers to key questions pertaining to Lp(a) that clinicians will find useful when assessing and treating patients (***see Box 1***). Much has been learned recently regarding Lp(a) structure, its possible causal association with ASCVD, and the impact of various treatments on Lp(a) levels. However, how to best use Lp(a) in risk stratification, assessment of risk across various ethnic groups, and whether lowering Lp(a) in the absence of lowering other atherogenic lipoproteins reduces ASCVD events remain as areas that need further investigation. Lastly, parallel efforts are needed in the clinical and the research community to standardize reporting of Lp(a) levels, so they are harmonized and comparable across laboratories and research studies.

Participating organizations

The following organizations participated in the Global Think Tank on the Clinical Considerations and Management of Lipoprotein(a), resulting in a series of deliverables including this consensus document to which each organization approves: Association of Black Cardiologists (ABC), American College of Cardiology (ACC), American Heart Association (AHA), European Atherosclerosis Society (EAS), International

Box 1
Answers to the top clinical questions.

Question	Answers
How should Lp(a) be measured?	• Lp(a) concentration assays (nmol/L) provide more accurate measurement than Lp(a) mass assays (mg/dL) • Converting measurements across assays can lead to over- or under-estimation of Lp(a) • Lp(a) assays need to be standardized against World Health Organization / International Federation of Clinical Chemistry and Laboratory Medicine (WHO/IFCC) reference material
What are the ethnic, gender, and age considerations?	• Elevated Lp(a) is independently associated with ASCVD in all racial and ethnic groups • Lp(a) levels are established early in childhood and remain relatively constant throughout life but may vary in some clinical conditions like acute coronary syndrome, diabetes, kidney or liver disease • Menopause is associated with an increase in plasma Lp(a) concentration given declining levels of estrogen • Cascade Lp(a) screening is considered reasonable when a patient with elevated Lp(a) is identified
How should Lp(a) be factored into risk assessment?	• Lp(a) measurement is useful in intermediate risk adults to reclassify ASCVD risk • Elevated Lp(a) levels are useful markers of increased ASCVD risk, suggesting the need for more aggressive lipid and non-lipid risk factor management in those with heterozygous FH, premature ASCVD, family history of premature ASCVD, recent acute coronary syndromes, or progressive ASCVD despite optimal medical management • Elevated Lp(a) levels may be associated with accelerated progression of aortic stenosis
What are the current and emerging treatment options for elevated Lp(a)?	• Available treatment options that lower Lp(a) include PCSK9 inhibitors and lipoprotein apheresis • Statins do not lower Lp(a) levels • Investigational agents that are associated with marked Lp(a) lowering are currently being investigated in secondary ASCVD prevention setting

Atherosclerosis Society (IAS), National Lipid Association (NLA), and Preventive Cardiovascular Nurses Association (PCNA).

Declaration of Competing Interest

JJS, CEO, LM, and AM have none. RDS has received honoraria outside this work related to consulting, speaker, or research activities from:

Abbott, Ache, Amgen, Amryt, Astra Zeneca, EMS, Esperion, Getz Pharma, Kowa, Hypera, MSD, Merck, Novartis, Novo-Nordisk, Pfizer, PTC Therapeutics, Roche and Sanofi. SV has received research support from the National Institutes of Health, Department of Veterans Affairs, World Heart Federation, Tahir and Jooma Family and honorarium from the American College of Cardiology in his role as the Associate Editor for Innovations (acc.org). MLK has received honoraria related to consulting, research and/or speaker activities from Ayma, Novartis, Abcentra, and Amgen. MDS has served on Scientific Advisory Boards with the following entities: Amgen, Novartis, Novo Nordisk.

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References

1. McCormick SP. Lipoprotein(a): biology and clinical importance. Clin Biochem Rev 2004;25(1):69-80. https://www.ncbi.nlm.nih.gov/pubmed/18516206.
2. Berg K. A new serum type system in man–the Lp system. Acta Pathol Microbiol Scand 1963;59:369-382. https://doi.org/10.1111/j.1699-0463.1963.tb01808.x.
3. Patel AP, Wang M, Pirruccello JP, et al. Lp(a) (Lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease: new insights from a large National Biobank. Arterioscler Thromb Vasc Biol 2021;41(1):465-474. https://doi.org/10.1161/ATVBAHA.120.315291.
4. Wilson DP, Jacobson TA, Jones PH, et al. Use of Lipoprotein(a) in clinical practice: a biomarker whose time has come. A scientific statement from the National Lipid Association. J Clin Lipidol 2019;13(3):374-392. https://doi.org/10.1016/j.jacl.2019.04.010.
5. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;139(25):e1046-e1081. https://doi.org/10.1161/CIR.0000000000000624.
6. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41(1):111-188. https://doi.org/10.1093/eurheartj/ehz455.
7. Pearson GJ, Thanassoulis G, Anderson TJ, et al. Canadian Cardiovascular Society Guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol 2021;2021. https://doi.org/10.1016/j.cjca.2021.03.016.
8. Marcovina SM, Albers JJ. Lipoprotein (a) measurements for clinical application. J Lipid Res 2016;57(4):526-537. https://doi.org/10.1194/jlr.R061648.
9. Kronenberg F, Utermann G. Lipoprotein(a): resurrected by genetics. J Intern Med 2013;273(1):6-30. https://doi.org/10.1111/j.1365-2796.2012.02592.x.
10. Tsimikas S, Clopton P, Brilakis ES, et al. Relationship of oxidized phospholipids on apolipoprotein B-100 particles to race/ethnicity, apolipoprotein(a) isoform size, and cardiovascular risk factors: results from the Dallas Heart Study. Circulation 2009;119(13):1711-1719. https://doi.org/10.1161/CIRCULATIONAHA.108.836940.
11. Marcovina SM, Clouet-Foraison N, Koschinsky ML, et al. Development of an LC-MS/MS proposed candidate reference method for the standardization of analytical methods to measure lipoprotein(a). Clin Chem 2021;67(3):490-499. https://doi.org/10.1093/clinchem/hvaa324.
12. Maeda S, Abe A, Seishima M, Makino K, Noma A, Kawade M. Transient changes of serum lipoprotein(a) as an acute phase protein. Atherosclerosis 1989;78(2–3):145-150. https://doi.org/10.1016/0021-9150(89)90218-9.
13. Muller N, Schulte DM, Turk K, et al. IL-6 blockade by monoclonal antibodies inhibits apolipoprotein (a) expression and lipoprotein (a) synthesis in humans. J Lipid Res 2015;56(5):1034-1042. https://doi.org/10.1194/jlr.P052209.
14. Yeang C, Witztum JL, Tsimikas S. "LDL-C" = LDL-C + Lp(a)-C: implications of achieved ultra-low LDL-C levels in the proprotein convertase subtilisin/kexin type 9 era of potent LDL-C lowering. Curr Opin Lipidol 2015;26(3):169-178. https://doi.org/10.1097/MOL.0000000000000171.
15. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med 2009;361(26):2518-2528. https://doi.org/10.1056/NEJMoa0902604.
16. Deo RC, Wilson JG, Xing C, et al. Single-nucleotide polymorphisms in LPA explain most of the ancestry-specific variation in Lp(a) levels in African Americans. PLoS One 2011;6(1). https://doi.org/10.1371/journal.pone.0014581.e14581.
17. Nikpay M, Goel A, Won HH, et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. Nat Genet 2015;47(10):1121-1130. https://doi.org/10.1038/ng.3396.
18. Cai DP, He YM, Yang XJ, Zhao X, Xu HF. Lipoprotein (a) is a risk factor for coronary artery disease in Chinese Han ethnic population modified by some traditional risk factors: a cross-sectional study of 3462 cases and 6125 controls. Clin Chim Acta 2015;451(Pt B):278-286. https://doi.org/10.1016/j.cca.2015.10.009.

19. Gambhir JK, Kaur H, Prabhu KM, Morrisett JD, Gambhir DS. Association between lipoprotein(a) levels, apo(a) isoforms and family history of premature CAD in young Asian Indians. Clin Biochem 2008;41(7–8):453-458. https://doi.org/10.1016/j.clinbiochem.2008.01.016.
20. Guan W, Cao J, Steffen BT, et al. Race is a key variable in assigning lipoprotein (a) cutoff values for coronary heart disease risk assessment: the Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol 2015;35(4):996-1001. https://doi.org/10.1161/ATVBAHA.114.304785.
21. Lanktree MB, Anand SS, Yusuf S, Hegele RA, Investigators S. Comprehensive analysis of genomic variation in the LPA locus and its relationship to plasma lipoprotein(a) in South Asians, Chinese, and European Caucasians. Circ Cardiovasc Genet 2010;3(1):39-46. https://doi.org/10.1161/CIRCGENETICS.109.907642.
22. Virani SS, Brautbar A, Davis BC, et al. Associations between lipoprotein(a) levels and cardiovascular outcomes in black and white subjects: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation 2012;125(2):241-249. https://doi.org/10.1161/CIRCULATIONAHA.111.045120.
23. Bittner V. Lipoprotein abnormalities related to women's health. Am J Cardiol 2002;90(8A):77i-84i. https://doi.org/10.1016/s0002-9149(02)02637-1.
24. Shlipak MG, Simon JA, Vittinghoff E, et al. Estrogen and progestin, lipoprotein(a), and the risk of recurrent coronary heart disease events after menopause. JAMA 2000;283(14):1845-1852. https://doi.org/10.1001/jama.283.14.1845.
25. Nowak-Gottl U, Strater R, Heinecke A, et al. Lipoprotein (a) and genetic polymorphisms of clotting factor V, prothrombin, and methylenetetrahydrofolate reductase are risk factors of spontaneous ischemic stroke in childhood. Blood 1999;94(11):3678-3682. https://www.ncbi.nlm.nih.gov/pubmed/10572079.
26. Burgess S, Ference BA, Staley JR, et al. Association of LPA variants with risk of coronary disease and the implications for lipoprotein(a)-lowering therapies: a Mendelian randomization analysis. JAMA Cardiol 2018;3(7):619-627. https://doi.org/10.1001/jamacardio.2018.1470.
27. Nave AH, Lange KS, Leonards CO, et al. Lipoprotein (a) as a risk factor for ischemic stroke: a meta-analysis. Atherosclerosis 2015;242(2):496-503. https://doi.org/10.1016/j.atherosclerosis.2015.08.021.
28. Langsted A, Nordestgaard BG, Kamstrup PR. Elevated lipoprotein(a) and risk of ischemic stroke. J Am Coll Cardiol 2019;74(1):54-66. https://doi.org/10.1016/j.jacc.2019.03.524.
29. Emerging Risk Factors C, Erqou S, Kaptoge S, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA 2009;302(4):412-423. https://doi.org/10.1001/jama.2009.1063.
30. Larsson SC, Gill D, Mason AM, et al. Lipoprotein(a) in Alzheimer, atherosclerotic, cerebrovascular, thrombotic, and valvular disease: Mendelian randomization investigation. Circulation 2020;141(22):1826-1828. https://doi.org/10.1161/CIRCULATIONAHA.120.045826.
31. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and improved cardiovascular risk prediction. J Am Coll Cardiol 2013;61(11):1146-1156. https://doi.org/10.1016/j.jacc.2012.12.023.
32. Consortium CAD, Deloukas P, Kanoni S, et al. Large-scale association analysis identifies new risk loci for coronary artery disease. Nat Genet 2013;45(1):25-33. https://doi.org/10.1038/ng.2480.
33. Willeit P, Kiechl S, Kronenberg F, et al. Discrimination and net reclassification of cardiovascular risk with lipoprotein(a): prospective 15-year outcomes in the Bruneck Study. J Am Coll Cardiol 2014;64(9):851-860. https://doi.org/10.1016/j.jacc.2014.03.061.
34. Lee SR, Prasad A, Choi YS, et al. LPA gene, ethnicity, and cardiovascular events. Circulation 2017;135(3):251-263. https://doi.org/10.1161/CIRCULATIONAHA.116.024611.
35. Nestel PJ, Barnes EH, Tonkin AM, et al. Plasma lipoprotein(a) concentration predicts future coronary and cardiovascular events in patients with stable coronary heart disease. Arterioscler Thromb Vasc Biol 2013;33(12):2902-2908. https://doi.org/10.1161/ATVBAHA.113.302479.
36. Perez de Isla L, Alonso R, Mata N, et al. Predicting cardiovascular events in familial hypercholesterolemia: The SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study). Circulation 2017;135(22):2133-2144. https://doi.org/10.1161/CIRCULATIONAHA.116.024541.
37. Albers JJ, Slee A, O'Brien KD, et al. Relationship of apolipoproteins A-1 and B, and lipoprotein(a) to cardiovascular outcomes: the AIM-HIGH trial (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes). J Am Coll Cardiol 2013;62(17):1575-1579. https://doi.org/10.1016/j.jacc.2013.06.051.
38. Khera AV, Everett BM, Caulfield MP, et al. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). Circulation 2014;129(6):635-642. https://doi.org/10.1161/CIRCULATIONAHA.113.004406.
39. Willeit P, Ridker PM, Nestel PJ, et al. Baseline and on-statin treatment lipoprotein (a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. Lancet 2018;392(10155):1311-1320. https://doi.org/10.1016/S0140-6736(18)31652-0.
40. Guddeti RR, Patil S, Ahmed A, et al. Lipoprotein(a) and calcific aortic valve stenosis: a systematic review. Prog Cardiovasc Dis 2020;63(4):496-502. https://doi.org/10.1016/j.pcad.2020.06.002.
41. Arsenault BJ, Boekholdt SM, Dube MP, et al. Lipoprotein(a) levels, genotype, and incident aortic valve stenosis: a prospective Mendelian randomization study and replication in a case-control cohort. Circ Cardiovasc Genet 2014;7(3):304-310. https://doi.org/10.1161/CIRCGENETICS.113.000400.
42. Capoulade R, Chan KL, Yeang C, et al. Oxidized phospholipids, lipoprotein(a), and progression of calcific aortic valve stenosis. J Am Coll Cardiol 2015;66(11):1236-1246. https://doi.org/10.1016/j.jacc.2015.07.020.
43. Tsimikas S, Gordts P, Nora C, Yeang C, Witztum JL. Statins and increases in Lp(a): an inconvenient truth that needs attention. Eur Heart J 2020;41(1):192-193. https://doi.org/10.1093/eurheartj/ehz776.
44. Roeseler E, Julius U, Heigl F, et al. Lipoprotein apheresis for lipoprotein(a)-associated cardiovascular disease: prospective 5 years of follow-up and apolipoprotein (a) characterization. Arterioscler Thromb Vasc Biol 2016;36(9):2019-2027. https://doi.org/10.1161/ATVBAHA.116.307983.
45. Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. J Am Coll Cardiol 2017;69(6):692-711. https://doi.org/10.1016/j.jacc.2016.11.042.
46. Verbeek R, Sandhu MS, Hovingh GK, et al. Lipoprotein(a) improves cardiovascular risk prediction based on established risk algorithms. J Am Coll Cardiol 2017;69(11):1513-1515. https://doi.org/10.1016/j.jacc.2017.01.017.
47. Orringer CE, Blaha MJ, Blankstein R, et al. The National Lipid Association scientific statement on coronary artery calcium scoring to guide preventive strategies for ASCVD risk reduction. J Clin Lipidol 2021;15(1):33-60. https://doi.org/10.1016/j.jacl.2020.12.005.
48. Mitchell JD, Fergestrom N, Gage BF, et al. Impact of statins on cardiovascular outcomes following coronary artery calcium scoring. J Am Coll Cardiol 2018;72(25):3233-3242. https://doi.org/10.1016/j.jacc.2018.09.051.
49. Nasir K. Message for 2018 cholesterol management guidelines update: time to accept the power of zero. J Am Coll Cardiol 2018;72(25):3243-3245. https://doi.org/10.1016/j.jacc.2018.10.006.
50. Ito MK, Santos RD. PCSK9 inhibition with monoclonal antibodies: modern management of hypercholesterolemia. J Clin Pharmacol 2017;57(1):7-32. https://doi.org/10.1002/jcph.766.
51. Vasquez N, Mehta A, Ayers C, et al. Lipoprotein(a) and coronary artery calcium score for predicting atherosclerotic cardiovascular disease risk. J Am Coll Cardiol 2020;75(11_Supplement_1):1846. https://doi.org/10.1016/S0735-1097(20)32473-6.
52. Gatto L, Prati F. Subclinical atherosclerosis: how and when to treat it? Eur Heart J Suppl 2020;22(Suppl E):E87-E90. https://doi.org/10.1093/eurheartj/suaa068.
53. Chasman DI, Shiffman D, Zee RY, et al. Polymorphism in the apolipoprotein(a) gene, plasma lipoprotein(a), cardiovascular disease, and low-dose aspirin therapy. Atherosclerosis 2009;203(2):371-376. https://doi.org/10.1016/j.atherosclerosis.2008.07.019.
54. Raber I, McCarthy CP, Vaduganathan M, et al. The rise and fall of aspirin in the primary prevention of cardiovascular disease. Lancet 2019;393(10186):2155-2167. https://doi.org/10.1016/S0140-6736(19)30541-0.
55. Bittner VA, Szarek M, Aylward PE, et al. Effect of alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. J Am Coll Cardiol 2020;75(2):133-144. https://doi.org/10.1016/j.jacc.2019.10.057.
56. O'Donoghue ML, Fazio S, Giugliano RP, et al. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. Circulation 2019;139(12):1483-1492. https://doi.org/10.1161/CIRCULATIONAHA.118.037184.
57. Szarek M, Bittner VA, Aylward P, et al. Lipoprotein(a) lowering by alirocumab reduces the total burden of cardiovascular events independent of low-density lipoprotein cholesterol lowering: ODYSSEY OUTCOMES trial. Eur Heart J 2020;41(44):4245-4255. https://doi.org/10.1093/eurheartj/ehaa649.
58. Lamina C, Kronenberg F, Lp GC. Estimation of the required lipoprotein(a)-lowering therapeutic effect size for reduction in coronary heart disease outcomes: a Mendelian randomization analysis. JAMA Cardiol 2019;4(6):575-579. https://doi.org/10.1001/jamacardio.2019.1041.
59. Greco MF, Sirtori CR, Corsini A, Ezhov M, Sampietro T, Ruscica M. Lipoprotein (a) lowering-from lipoprotein apheresis to antisense oligonucleotide approach. J Clin Med 2020;9(7). https://doi.org/10.3390/jcm9072103.
60. Santos RD, Raal FJ, Catapano AL, Witztum JL, Steinhagen-Thiessen E, Tsimikas S. Mipomersen, an antisense oligonucleotide to apolipoprotein B-100, reduces lipoprotein(a) in various populations with hypercholesterolemia: results of 4 phase III trials. Arterioscler Thromb Vasc Biol 2015;35(3):689-699. https://doi.org/10.1161/ATVBAHA.114.304549.
61. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, et al. Lipoprotein (a) reduction in persons with cardiovascular disease. N Engl J Med 2020;382(3):244-255. https://doi.org/10.1056/NEJMoa1905239.
62. Jia X, Liu J, Mehta A, Ballantyne CM, Virani SS. Lipid-lowering biotechnological drugs: from monoclonal antibodies to antisense therapies-a clinical perspective. Cardiovasc Drugs Ther 2020. https://doi.org/10.1007/s10557-020-07082-x.
63. Sahebkar A, Simental-Mendia LE, Pirro M, et al. Impact of ezetimibe on plasma lipoprotein(a) concentrations as monotherapy or in combination with statins: a systematic review and meta-analysis of randomized controlled trials. Sci Rep 2018;8(1):17887. https://doi.org/10.1038/s41598-018-36204-7.
64. Parish S, Hopewell JC, Hill MR, et al. Impact of apolipoprotein(a) isoform size on lipoprotein(a) lowering in the HPS2-THRIVE study. Circ Genom Precis Med 2018;11(2). https://doi.org/10.1161/CIRCGEN.117.001696.e001696.
65. Duell PB, Santos RD, Kirwan BA, Witztum JL, Tsimikas S, Kastelein JJP. Long-term mipomersen treatment is associated with a reduction in cardiovascular events in patients with familial hypercholesterolemia. J Clin Lipidol 2016;10(4):1011-1021. https://doi.org/10.1016/j.jacl.2016.04.013.