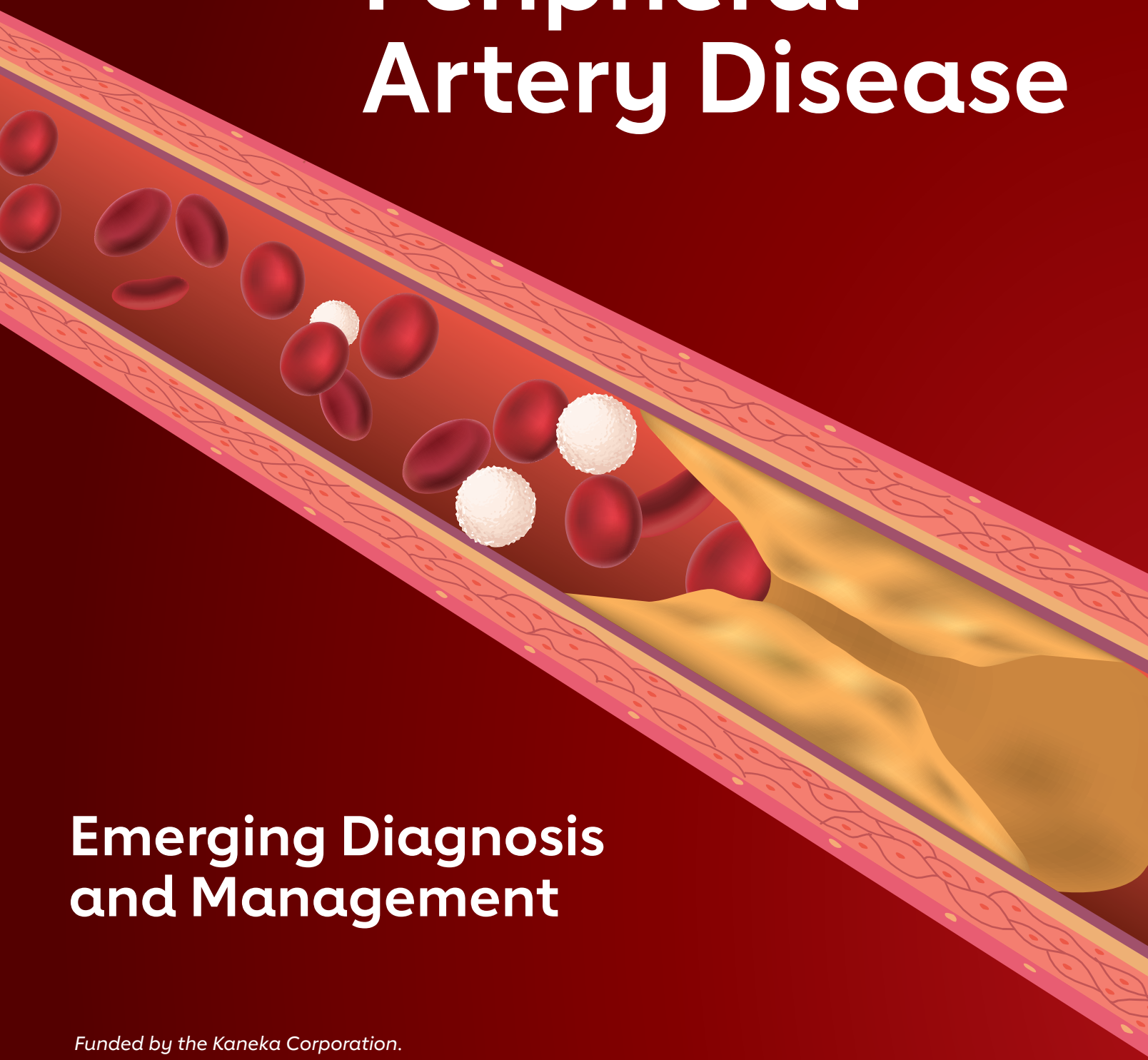
American Heart Association.

Lp(a) and Peripheral Artery Disease



Emerging Diagnosis and Management

Funded by the Kaneka Corporation.

Publisher's Note
The Lp(a) and PAD: Emerging Diagnosis and Management is published by Ascend Media.
401 SW Ward Road, Suite 210, Lee's Summit, MO 64081

All references and data are as of July 2024.

Contents

Contributing Authors

Danielle Vlazny, PA-C, MS, CWS, FSVM, is a physician assistant, assistant professor with the Gonda Vascular Center at Mayo Clinic Rochester, Minnesota. She has provided care to vascular patients over the past eight years in outpatient general vascular medicine, thrombophilia, vein clinic, wound care, and inpatient consulting service. In addition, she works on numerous evidence-based medicine and quality improvement projects within the center and teaches at the Mayo Clinic Physician Assistant Program.

Disclosures:

Professional Services and Activities – Employment: Mayo Clinic

Professional Services and Activities – Other Professional Activities: Mayo Foundation for Medical Education and Research

Nkechinyere (Nkechi) Ijioma, MBBS, FAHA, FACC, is an interventional cardiologist, and assistant professor of medicine at The Ohio State University. Her research interests include endovascular interventions, acute coronary syndrome, and cardiovascular health equity. Dr. Ijioma currently serves as the program director of Peripheral Vascular Interventions in the Division of Cardiovascular Medicine at The Ohio State University Wexner Medical Center.

Disclosures:

Professional Services and Activities – Employment: The Ohio State University Wexner Medical Center

John Giacona, PA-C, PhD, is a physician assistant at the University of Texas Southwestern Medical Center. Dr. Giacona practices in the Hypertension Section within the Division of Cardiology – Department of Internal Medicine. His research interests include high-density lipoprotein metabolism, skeletal muscle mitochondrial function, and the autonomic control of blood pressure. Dr. Giacona currently serves as chair of Preventive Cardiology for the Academy of Physician Associates in Cardiology.

Reported no disclosures

Geoffrey Barnes, MD, MSc, FAHA, is a cardiologist and vascular medicine specialist at the University of Michigan Frankel Cardiovascular Center. Dr. Barnes is an NIH-funded health services researcher who is active in advancing the care of patients with thrombotic conditions, including peripheral artery disease. He is a leader with several national societies and currently serves as the fellowship director for the University of Michigan Vascular Medicine Fellowship program.

Disclosures:

Professional Services and Activities – Employment: University of Michigan

Professional Services and Activities – Consultant: Acelis Connected Health, Bayer, Janssen Biotech, Inc., AstraZeneca, Pfizer, Anthos, Bristol-Myers Squibb, Sanofi, Abbott Vascular

Financial Support – Grant/Contract: Boston Scientific Corporation

Heather Harker Ryan, RN, PhD, CPN, FPCNA, is the clinical nurse educator and nurse scientist for the ambulatory division of the Cambridge Health Alliance in Cambridge, Massachusetts. Her program of research focuses on the identification and treatment of children and families affected by familial hypercholesterolemia. She currently holds leadership positions in a number of national organizations related to nursing leadership and cardiovascular care.

Disclosures:

Professional Services and Activities – Employment: Cambridge Health Alliance, Massachusetts General Hospital, University of Massachusetts Boston, Boston Children's Hospital

P. Barton Duell, MD, FAHA, MNLA, is an endocrinologist and lipid specialist at the Oregon Health & Science University where he is a professor of medicine in the Center for Preventive Cardiology, Knight Cardiovascular Institute and the Division of Endocrinology, Diabetes, and Clinical Nutrition. He is the director of the Lipoprotein Apheresis Unit and Sterol Analysis Laboratory at OHSU, as well as the co-editor-in-chief of the *Journal of Clinical Lipidology*. He serves/has served in leadership roles in various organizations including the AHA. He has been involved in numerous phase I-IV research studies related to lipid metabolism and ASCVD risk and has been evaluating and treating patients with elevated Lp(a) for more than 35 years.

Disclosures:

Professional Services and Activities – Employment: Oregon Health & Science University

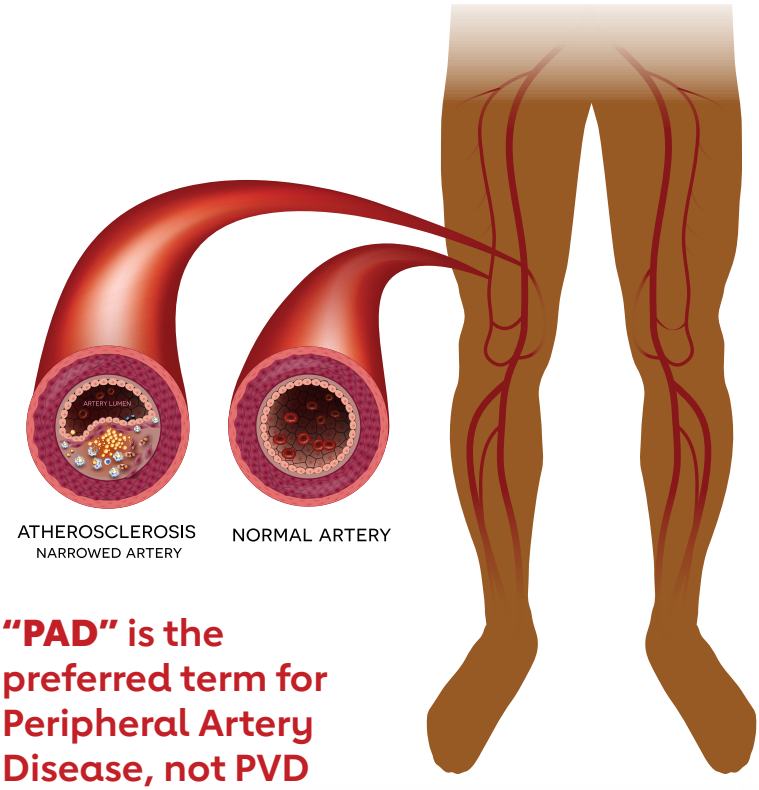
Professional Services and Activities – Consultant: Esperion Therapeutics Inc., Kaneka Pharma America LLC, Novo Nordisk, Regeneron Pharmaceuticals, Travere Therapeutics, Inc.

Professional Services and Activities – Data and Safety Monitoring: Ionis

Financial Support – Grant/Contract: Boston Scientific Corporation

Defining PAD

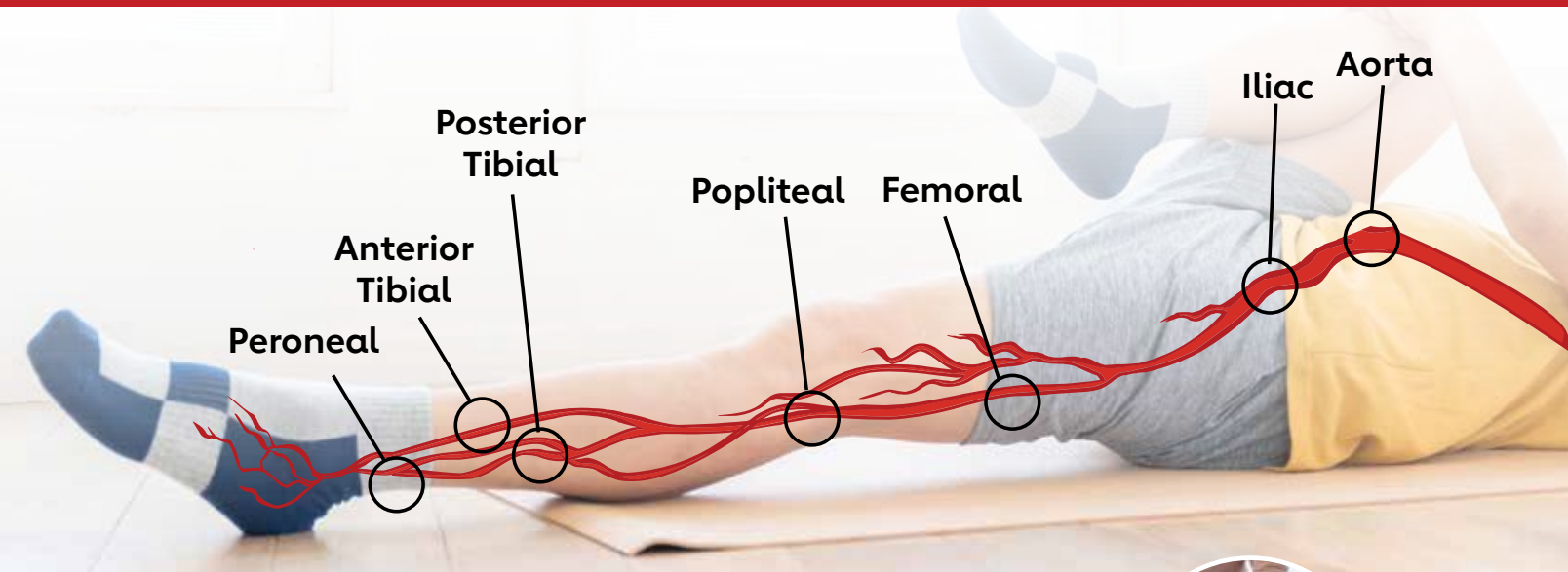
Peripheral artery disease refers to peripheral artery obstruction secondary to atherosclerotic disease.



~~PVD~~

"PAD" is the preferred term for Peripheral Artery Disease, not PVD

Arteries Most Commonly Affected by PAD



*PAD most commonly affects the lower extremities, but **can also affect the upper extremities**.*

Risk Factors for PAD

- Older age
- Diabetes
- Smoking
- Family history of PAD
- Chronic Kidney Disease (CKD)
- Hyperlipidemia
- Hypertension
- Atherosclerotic disease in another vascular bed

Prevalence of PAD

In the U.S., approximately **10–12M people age 40+** have PAD.[1, 2, 3]

Lifetime risk of PAD

(80-year horizon)

was estimated at: [3, 4, 5]

19% White people

22% Hispanic people

29% Black people

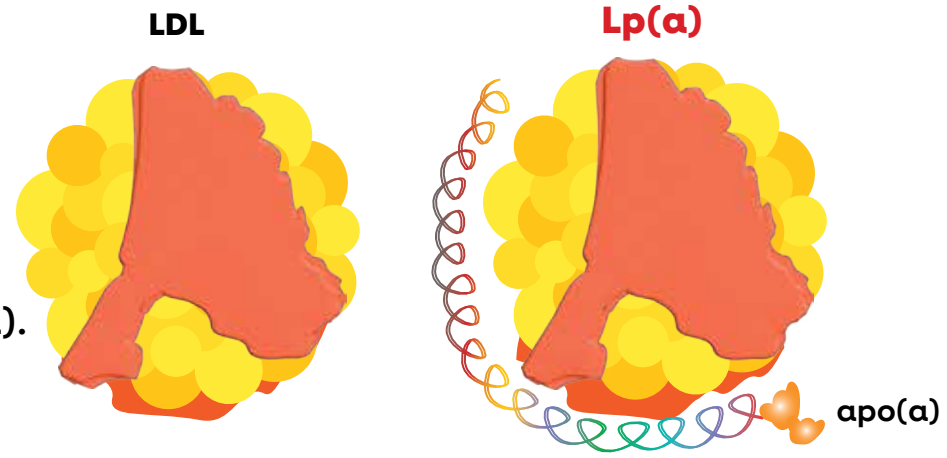
PAD is overrepresented in the Black community.

Complications

of PAD are called major adverse limb events (**MALE**) and may include recurrent limb ischemia and/or amputation.

Defining Lp(a) *and Why It Matters*

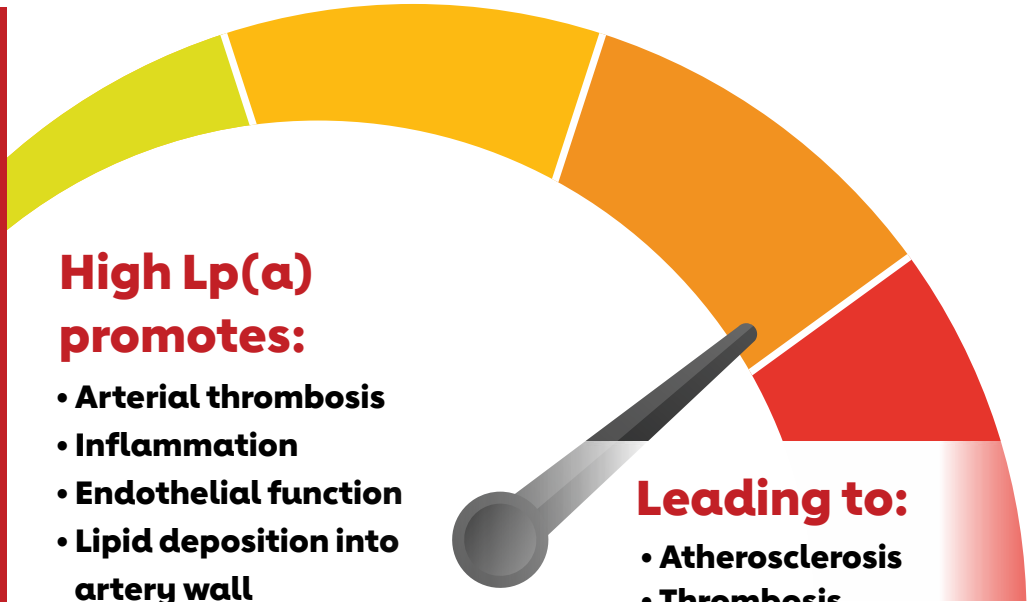
Lipoprotein(a) – Lp(a) – is composed of an LDL-like moiety that is covalently bound to apolipoprotein(a) – apo(a).



Lp(a) is:

80-90%
Genetically determined [6, 7, 8]

While not completely defined, Lp(a) is believed to be produced in the liver with proinflammatory and proatherogenic properties.



High Lp(a) promotes:

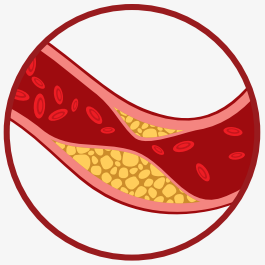
- Arterial thrombosis
- Inflammation
- Endothelial function
- Lipid deposition into artery wall

Leading to:

- Atherosclerosis
- Thrombosis
- Calcific aortic stenosis

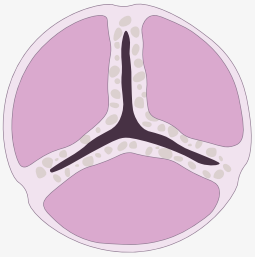
Epigenetic studies show an association between elevated Lp(a) levels and atherosclerotic cardiovascular disease (ASCVD). [9, 10]

Disease/condition



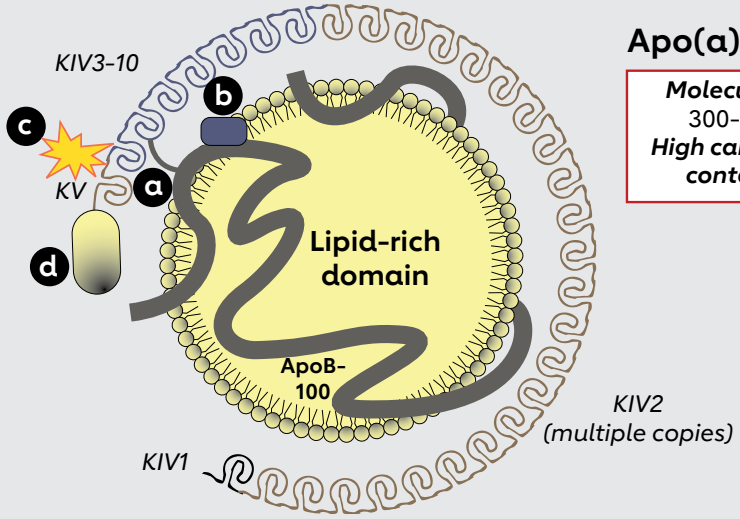
Atherosclerosis

Thrombosis



Aortic Valve Calcification

Lp(a) structure & property



Apo(a)

Molecular mass: 300-800 kDa
High carbohydrate content: 28%

Regulation

Lp(a) concentration (high variability)

- *Genetics*
- *Ethnicity/ Race*
- *Medical conditions*
- *Environment*

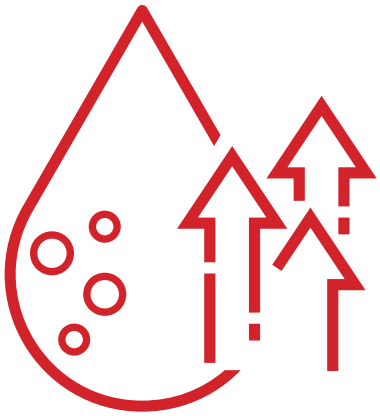
Lp(a) serum level is associated with atherosclerotic cardiovascular diseases including stroke, myocardial infarction (MI), and PAD. Lp(a) is also a significant independent risk factor for PAD and is associated with more severe forms of PAD in specific populations.[4]

An estimated 20-25% of the world's population has elevated levels of Lp(a).[11]

Why Is Lp(a) Important to Measure in Addition to LDL?

Elevated Lp(a) is an independent risk factor for coronary heart disease (CHD), PAD, cerebrovascular disease, and calcific aortic stenosis.

Why would a clinician measure Lp(a)?



Elevated Lp(a) is a common independent atherosclerotic cardiovascular disease risk factor that is not measured in the majority of affected patients.

The only currently available method to know if someone has elevated Lp(a) is to measure Lp(a) with a simple blood test that is relatively inexpensive.

Awareness of the presence of elevated Lp(a) is important, because high Lp(a) increases atherosclerotic cardiovascular disease risk and could inform clinical decision-making regarding risk management.

Cascade screening of family members of patients with elevated Lp(a) may identify additional individuals with elevated Lp(a) because of its autosomal codominant inheritance pattern.[12]

Lp(a) can be increased by:[13]

a) CKD

b) Liver disease

c) Menopause

Raising Awareness of Lp(a)

Once an individual's Lp(a) levels are tested, do they need to be retested?

Although levels are generally stable over time, the levels can vary between labs or may increase after development of certain medical conditions, may decrease after treatment, and may otherwise vary. It may also be helpful to verify results with an outside lab before initiating therapies.

Who to test?

2018 Guideline on the Management of Blood Cholesterol states the relative indications for measurement are family history of premature ASCVD or personal history of ASCVD not explained by major risk factors.[14, 15, 16, 17]

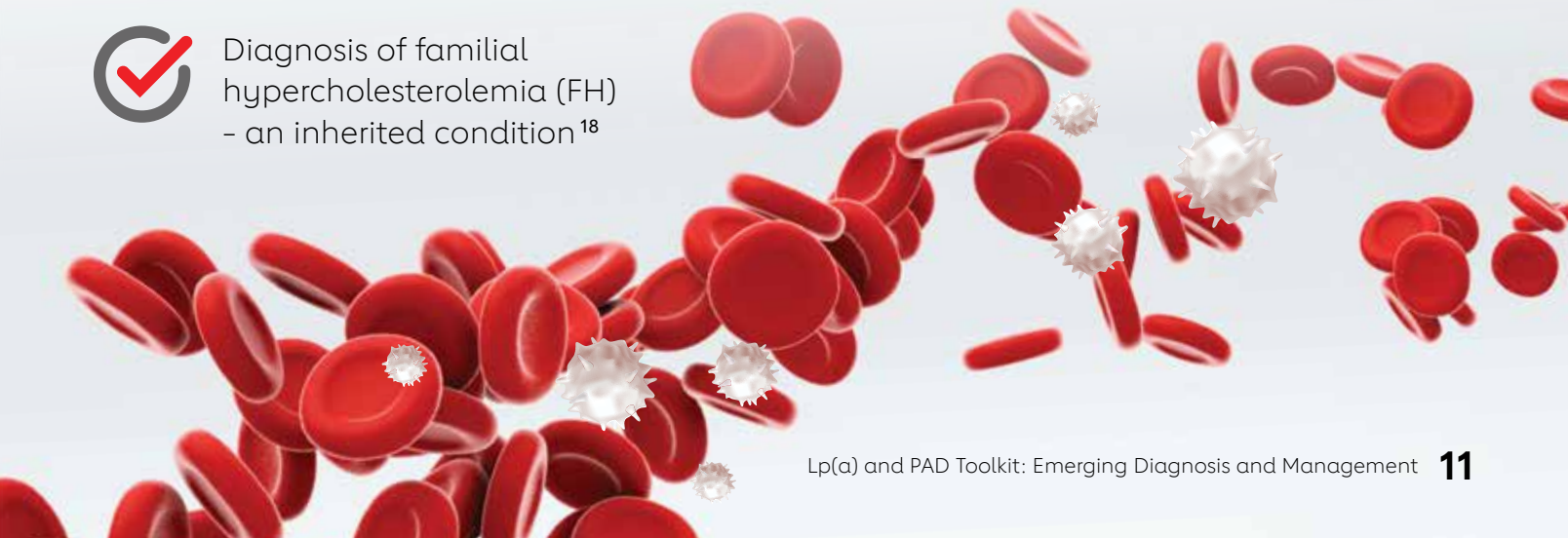
- Those with borderline ASCVD risk to aid in discussion of risk modification therapies
- Family or personal history of high Lp(a), heart disease, or premature cardiovascular disease
- Diagnosis of familial hypercholesterolemia (FH) - an inherited condition[18]

How should one measure Lp(a)?[12]

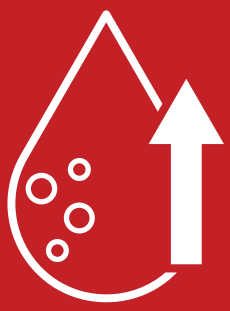
Lp(a) should be measured with:

- An isoform-insensitive assay
- Assay that is traceable to the internationally accepted calibrator (World Health Organization/International Federation of Clinical Chemistry Reference Material SRM-2B)
- Assay that is reported in nanomoles per liter (nmol/l), when possible.

If measurements are not uniformly calibrated, one cannot compare measurements generated by different assays.



Intersection of Lp(a) With PAD



Lp(a) and Major Adverse Cardiovascular Event (MACE)

Elevated Lp(a) levels are independently associated with incident MACE and MALE in patients with PAD treated with revascularization irrespective of LDL-cholesterol (LDL-C) level and statin administration.[12]

Higher Lp(a) levels are independently associated with an increased risk of MALE in hospitalized patients.[4]

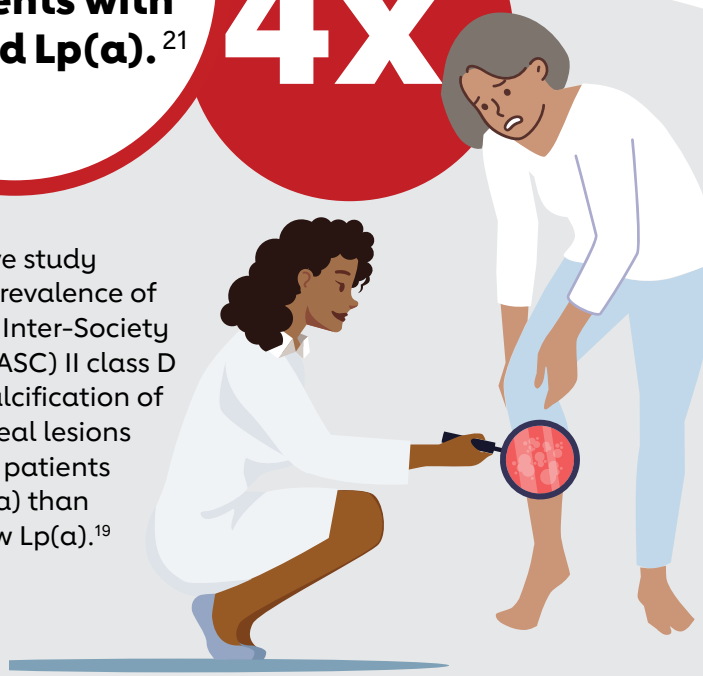
Findings from mechanistic, observational, and genetic studies support the causal role of Lp(a) in CVD, including CHD and PAD.[19]

Elevated Lp(a) levels are associated with an increased risk of MALE in hospitalized patients.[20]

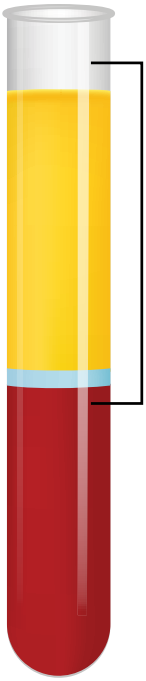
MALE is 4 times more common in patients with elevated Lp(a).[21]

4x

A retrospective study showed the prevalence of TransAtlantic Inter-Society Consensus (TASC) II class D and severe calcification of femoropopliteal lesions was higher in patients with high Lp(a) than those with low Lp(a).[19]



High Lp(a) Is Associated With Increased MALE.[21]

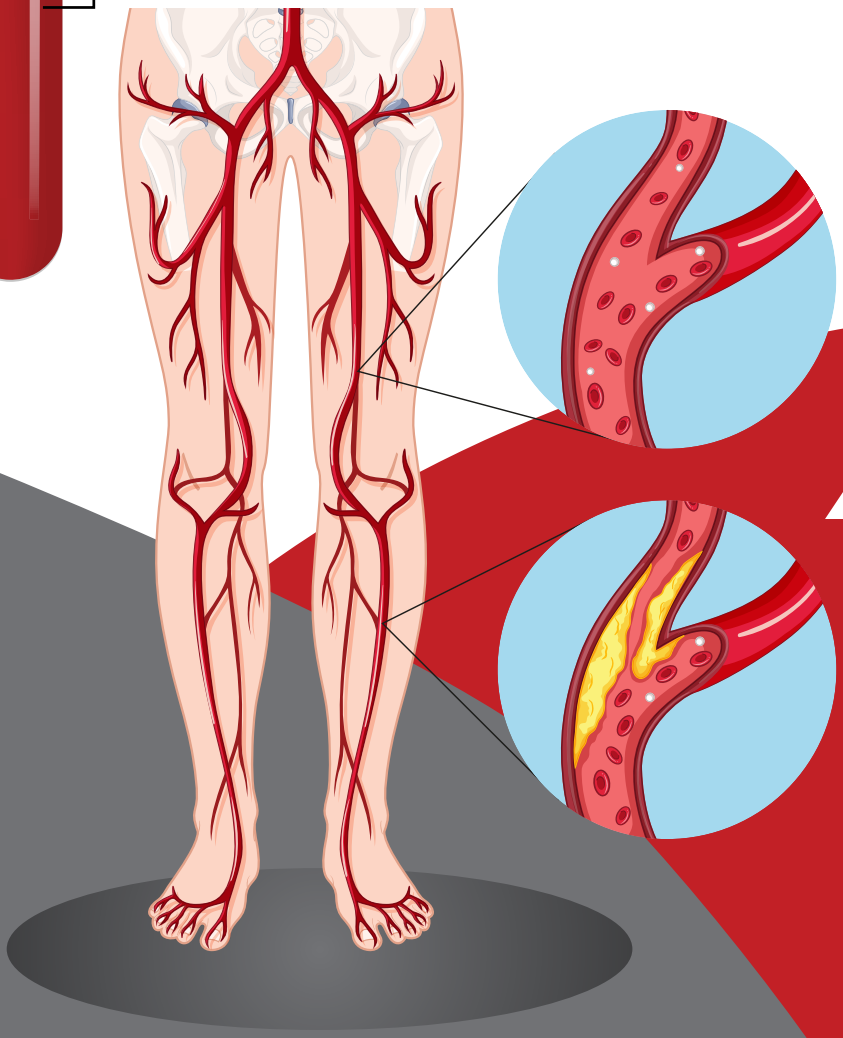


Plasma Lp(a) is independently associated with first and consecutive MALE after iliofemoral endarterectomy. [22]

Elevated Lp(a) increases risk for MALE post-revascularization in

67.9%

of patients with PAD at 5 years regardless of LDL level and statin use (HR 4.15).[21]



Elevated Lp(a) incurs a

33%

higher risk of lower extremity revascularization in patients with PAD.[23]

Approaches for Lowering Lp(a)

Lipoprotein Apheresis lowers Lp(a) acutely by **50-85%**[12]

- FDA approved for patients with familial hypercholesterolemia who have ASCVD (such as MI, PAD, CVD) and LDL-C > 100 mg/dl on maximal tolerable drug and lifestyle therapy with or without Lp(a) > 60 mg/dl.[12]
- Indirect evidence suggests that Lp(a) lowering with Lipoprotein Apheresis may be associated with decreased ASCVD risk.[24]
- Results in **improved circulation, pain level, and walking distance** in those with elevated Lp(a) and severe PAD.[25]
- **May reduce CV events** in FH patients with elevated Lp(a) ≥60 mg/dL. [26, 27]

PCSK9 Inhibitors reduce Lp(a) up to **30%**[17]

- Data from trials of monoclonal antibodies directed against PCSK9 demonstrated dramatic LDL-C lowering by an average of 50% to 60%, but also modest Lp(a) lowering of 25% to 30%.[28]
- **FOURIER** trial: The PCSK9 inhibitor (PCSK9i) evolocumab lowered Lp(a) by a median of **27%** at **48 weeks**.[14, 29]
- **ODYSSEY OUTCOMES** trial: 18,924 patients with recent acute coronary syndrome who were taking high-intensity statin demonstrated that the PCSK9i alirocumab reduced Lp(a) by **23%** after **4 months**.[30]
- **ORION-11** (inclisiran) trial:[31] The placebo-corrected percentage reduction in Lp(a) levels from **baseline to Day 540** was **28.5%**.

We currently lack definitive proof that specific pharmacological lowering of Lp(a) reduces adverse cardiovascular outcomes. Many clinicians have the secondary goal of lowering Lp(a) in addition to lowering LDL-C and Apolipoprotein B (ApoB) in high-risk patients, in particular, when recurrent ASCVD events occur despite aggressive LDL-C lowering.[12]

Emerging Experimental Therapies

for Lp(a)

Antisense Oligonucleotide (ASO)

a. **Pelacarsen** - may lower Lp(a) by about 80%

CETP inhibitor

a. **Obicetrapib** - may lower Lp(a) by about 45%

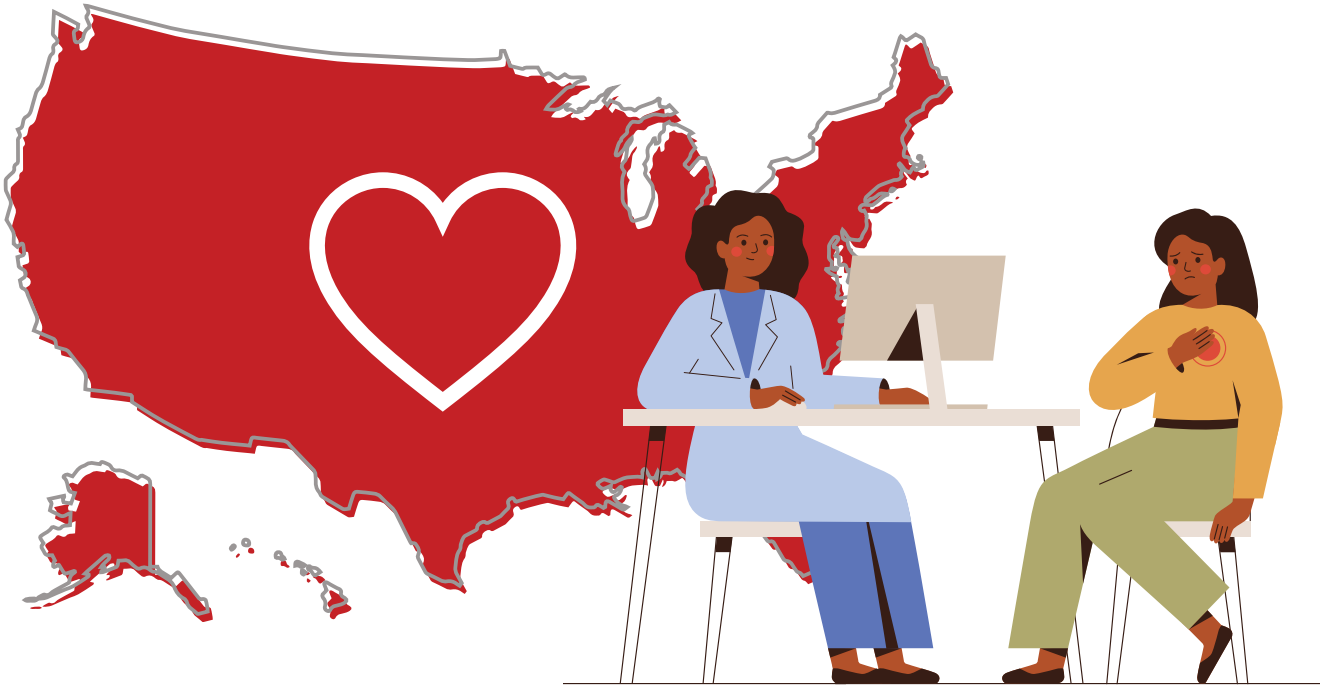
Small interfering RNA (siRNA)

a. **Olpasiran** - dose-dependent reduction with ASCVD [32]
b. **SLN360** – dose-dependent reduction of Lp(a) [33]
c. **Lepodisiran** – dose-dependent, long-duration reductions in serum Lp(a) concentrations [34]

What Can Health Care Professionals (HCPs) Do Now?

Shared Decision-Making [35]

- Relative indications for measuring Lp(a) are family history of premature ASCVD or personal history of ASCVD not explained by major risk factors.
- Verify insurance coverage of testing and treatments.
- Discuss new therapies in development.
- Intensify management of all other ASCVD risk factors, including LDL-C and non-HDL-C elevation. If measured, the Lp(a) level can be used as a risk-enhancing factor in this scenario.[12]



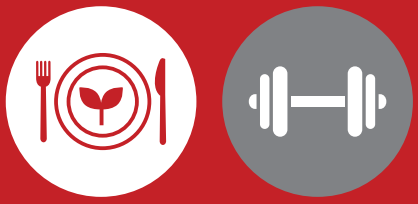
Treat modifiable risk factors

Medical therapy and lifestyle changes include targeting diabetes (enhanced glucose control), smoking cessation, treating HTN and/or high LDL-C, sustained weight loss, and increasing physical activity.[6]

Initiate or increase statin intensity if elevated Lp(a), even if LDL-C is at goal.

Lp(a) lowering is difficult, but proven therapies for ASCVD prevention should be implemented.

Lp(a) levels are 80-90% genetically influenced.[6]



Diet and exercise have not been shown to reduce Lp(a) levels.[5, 12]

Follow the Guidelines

- 2019 AHA/ACC primary prevention of CVD.[6]
- An Lp(a) ≥50 mg/dL or ≥125 nmol/L is considered a risk-enhancing factor.[12]

Cascade screening of family members of a patient with high Lp(a) will identify elevated Lp(a) in family members. This allows affected family members to learn they have a hidden ASCVD risk factor, and provides an opportunity for them to intensify ASCVD preventive interventions.[12]

Top Takeaways

1. Lp(a) is largely determined by genetics.

2. Lp(a) is elevated in approximately 20% of the general population. Elevated Lp(a) is overrepresented in the Black community.

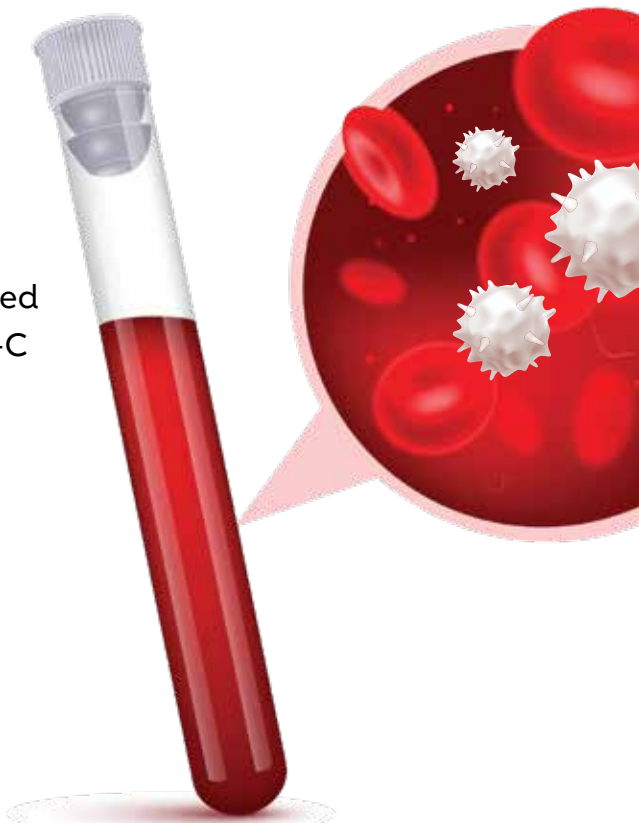
3. Lp(a) elevation is known to drive atherosclerosis and intravascular inflammation, increasing the risk for ASCVD and PAD.

4. Patients with elevated Lp(a) have worse outcomes related to PAD and high incidence of MALE.

5. Patients with PAD are candidates for screening for Lp(a) elevation.

6. Lipoprotein Apheresis is currently the sole FDA-approved treatment for lowering Lp(a), only in individuals with clinically diagnosed Familial Hypercholesterolemia with documented coronary or peripheral artery disease and LDL-C levels greater than 100 mg/dL.[36]

7. Therapies to reduce Lp(a) levels are in development.



Notes:

Notes:

Glossary

Apo(a) . . . . . Apolipoprotein(a)

ApoB . . . . . Apolipoprotein B

ASCVD . . . . . Atherosclerotic Cardiovascular Disease

CHD . . . . . Coronary Heart Disease

CKD . . . . . Chronic Kidney Disease

FH . . . . . Familial Hypercholesterolemia

HCP . . . . . Health Care Professionals

HoFH . . . . . Homozygous Familial Hyperlipidemia

LDL-C . . . . . Low Density Lipoprotein Cholesterol

Lp(a) . . . . . Lipoprotein(a) (pronounced L-P-little-A) [36]

MACE . . . . . Major Adverse Cardiovascular Event

MALE . . . . . Major Adverse Limb Event

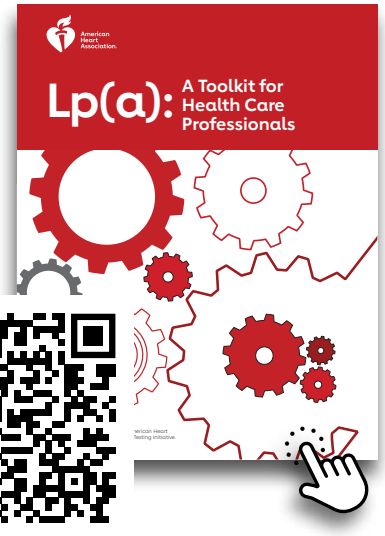
PAD . . . . . Peripheral Artery Disease

PVD . . . . . Peripheral Vascular Disease

PCSK9 inhibitors . . . . . PCSK9 Monoclonal Antibody

siRNA . . . . . Small Interfering RNA

TASC . . . . . TransAtlantic Inter-Society Consensus



For more information on Lp(a), scan the QR code to download *Lp(a): A Toolkit for Health Care Professionals.*

References

1. Virani, Salim S et al. "Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association." *Circulation* vol. 143,8 (2021): e254-e743. doi:10.1161/CIR.0000000000000950
2. Criqui, Michael H et al. "Lower Extremity Peripheral Artery Disease: Contemporary Epidemiology, Management Gaps, and Future Directions: A Scientific Statement From the American Heart Association." *Circulation* vol. 144,9 (2021): e171-e191. doi:10.1161/CIR.0000000000001005
3. Gornik, Heather L et al. "2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines." *Circulation* vol. 149,24 (2024): e1313-e1410. doi:10.1161/CIR.0000000000001251
4. Guédon, Alexis F et al. "Association of Lipoprotein(a) Levels With Incidence of Major Adverse Limb Events." *JAMA Network Open* vol. 5,12 e2245720. 1 Dec. 2022, doi:10.1001/jamanetworkopen.2022.45720
5. Enkhmaa, Byambaa et al. "Diet and Lp(a): Does Dietary Change Modify Residual Cardiovascular Risk Conferred by Lp(a)?." *Nutrients* vol. 12,7 2024. 7 Jul. 2020, doi:10.3390/nu12072024
6. Arnett, Donna K et al. "2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines." *Circulation* vol. 140,11 (2019): e596-e646. doi:10.1161/CIR.0000000000000678
7. Duarte Lau, Freddy, and Robert P Giugliano. "Lipoprotein(a) and its Significance in Cardiovascular Disease: A Review." *JAMA Cardiology* vol. 7,7 (2022): 760-769. doi:10.1001/jamacardio.2022.0987
8. Tsimikas, Sotirios. "A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies." *Journal of the American College of Cardiology* vol. 69,6 (2017): 692-711. doi:10.1016/j.jacc.2016.11.042
9. Tipping, Robert W et al. "Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality." *JAMA* vol. 302,4 (2009): 412-23. doi:10.1001/jama.2009.1063
10. Patel, Aniruddh P et al. "Lp(a) (Lipoprotein[a]) Concentrations and Incident Atherosclerotic Cardiovascular Disease: New Insights From a Large National Biobank." *Arteriosclerosis, Thrombosis, and Vascular Biology* vol. 41,1 (2021): 465-474. doi:10.1161/ATVBAHA.120.315291
11. Tsimikas, Sotirios, and Santica M Marcovina. "Ancestry, Lipoprotein(a), and Cardiovascular Risk Thresholds: JACC Review Topic of the Week." *Journal of the American College of Cardiology* vol. 80,9 (2022): 934-946. doi:10.1016/j.jacc.2022.06.019
12. Reyes-Soffer, Gissette et al. "Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease: A Scientific Statement From the American Heart Association." *Arteriosclerosis, Thrombosis, and Vascular Biology* vol. 42,1 (2022): e48-e60. doi:10.1161/ATV.0000000000000147
13. Enkhmaa B, Berglund L. Non-genetic influences on lipoprotein(a) concentrations. *Atherosclerosis*. 2022 May;349:53-62. doi: 10.1016/j.atherosclerosis.2022.04.006. PMID: 35606076; PMCID: PMC9549811.
14. Grundy, Scott M et al. "2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines." *Circulation* vol. 139,25 (2019): e1082-e1143. doi:10.1161/CIR.0000000000000625
15. Koschinsky ML, Bajaj A, Boffa MB, Dixon DL, Ferdinand KC, Gidding SS, Gill EA, Jacobson TA, Michos ED, Safarova MS, Soffer DE, Taub PR, Wilkinson MJ, Wilson DP, Ballantyne CM. A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice. *J Clin Lipidol*. 2024 May-Jun;18(3):e308-e319. doi: 10.1016/j.jacl.2024.03.001
16. Pearson GJ, Thanassoulis G, Anderson TJ, Barry AR, Couture P, Dayan N, Francis GA, Genest J, Grégoire J, Grover SA, Gupta M, Hegele RA, Lau D, Leiter LA, Leung AA, Lonn E, Mancini GBJ, Manjoo P, McPherson R, Ngui D, Piché ME, Poirier P, Sievenpiper J, Stone J, Ward R, Wray W. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. *Can J Cardiol*. 2021 Aug;37(8):1129-1150. doi: 10.1016/j.cjca.2021.03.016
17. Mach, Francois et al. 2019 ESC/EAS Guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *European Heart Journal* vol. 41, Issue 1, (2020). https://doi.org/10.1093/eurheartj/ehz455
18. Farzam K, Zubair M, Senthilkumaran S. Lipoprotein A. [Updated 2024 Feb 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK570621/
19. Yanaka, Koji et al. "Relationship Between Lipoprotein(a) and Angiographic Severity of Femoropopliteal Lesions." *Journal of Atherosclerosis and Thrombosis* vol. 28,5 (2021): 555-561. doi:10.5551/jat.56457
20. Kamstrup, Pia R. "Lipoprotein(a) and Cardiovascular Disease." *Clinical Chemistry* vol. 67,1 (2021): 154-166. doi:10.1093/clinchem/hvaa247
21. Tomoi, Yusuke et al. "Impact of High Lipoprotein(a) Levels on Clinical Outcomes Following Peripheral Endovascular Therapy." *JACC. Cardiovascular Interventions* vol. 15,14 (2022): 1466-1476. doi:10.1016/j.jcin.2022.05.050
22. Verwer, Maarten C et al. "High lipoprotein(a) is associated with major adverse limb events after femoral artery endarterectomy." *Atherosclerosis* vol. 349 (2022): 196-203. doi:10.1016/j.atherosclerosis.2021.11.019
23. Golledge, Jonathan et al. "Association of Serum Lipoprotein (a) With the Requirement for a Peripheral Artery Operation and the Incidence of Major Adverse Cardiovascular Events in People With Peripheral Artery Disease." *Journal of the American Heart Association* vol. 9,6 (2020): e015355. doi:10.1161/JAHA.119.015355
24. Schwartz, Gregory G. et al. "Lipoprotein(a) and Benefit of PCSK9 Inhibition in Patients With Nominally Controlled LDL Cholesterol." *JACC* vol. 78, 5 (2021): doi/10.1016/j.jacc.2021.04.102
25. Poller, Wolfram C et al. "Lipoprotein apheresis in patients with peripheral artery disease and hyperlipoproteinemia(a)." *Atherosclerosis. Supplements* vol. 18 (2015): 187-93. doi:10.1016/j.atherosclerosissup.2015.02.032
26. Roeseler, Eberhard et al. "Lipoprotein Apheresis for Lipoprotein(a)-Associated Cardiovascular Disease: Prospective 5 Years of Follow-Up and Apolipoprotein(a) Characterization." *Arteriosclerosis, Thrombosis, and Vascular Biology* vol. 36,9 (2016): 2019-27. doi:10.1161/ATVBAHA.116.307983
27. Leebmann, Josef et al. "Lipoprotein apheresis in patients with maximally tolerated lipid-lowering therapy, lipoprotein(a)-hyperlipoproteinemia, and progressive cardiovascular disease: prospective observational multicenter study." *Circulation* vol. 128,24 (2013): 2567-76. doi:10.1161/CIRCULATIONAHA.113.002432
28. Shapiro MD, Minnier J, Tavori H, Kassahun H, Flower A, Somaratne R, Fazio S. Relationship Between Low-Density Lipoprotein Cholesterol and Lipoprotein(a) Lowering in Response to PCSK9 Inhibition With Evolocumab. *J Am Heart Assoc.* 2019 Feb 19;8(4):e010932. doi: 10.1161/JAHA.118.010932. PMID: 30755061; PMCID: PMC6405654. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6405654/
29. Bittner, Vera A et al. "Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome." *Journal of the American College of Cardiology* vol. 75,2 (2020): 133-144. doi:10.1016/j.jacc.2019.10.057
30. Ray, Kausik K et al. "Effect of inclisiran on lipids in primary prevention: the ORION-11 trial." *European Heart Journal* vol. 43,48 (2022): 5047-5057. doi:10.1093/eurheartj/ehac615
31. Franchini, Massimo et al. "Lipoprotein apheresis for the treatment of elevated circulating levels of lipoprotein(a): a critical literature review." *Blood transfusion = Trasfusione del sangue* vol. 14,5 (2016): 413-8. doi:10.2450/2015.0163-15
32. O'Donoghue, Michelle L et al. "Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease." *The New England Journal of Medicine* vol. 387,20 (2022): 1855-1864. doi:10.1056/NEJMoa2211023
33. Nissen, Steven E et al. "Single Ascending Dose Study of a Short Interfering RNA Targeting Lipoprotein(a) Production in Individuals With Elevated Plasma Lipoprotein(a) Levels." *JAMA* vol. 327,17 (2022): 1679-1687. doi:10.1001/jama.2022.5050
34. Nissen, Steven E et al. "Lepodisiran, an Extended-Duration Short Interfering RNA Targeting Lipoprotein(a): A Randomized Dose-Ascending Clinical Trial." *JAMA* vol. 330,21 (2023): 2075-2083. doi:10.1001/jama.2023.21835
35. Dennison Himmelfarb, et al. "Shared Decision-Making and Cardiovascular Health: A Scientific Statement From the American Heart Association." *Circulation* vol. 148,11 (2023): 912-931. doi:10.1161/CIR.0000000000001162
36. Centers for Disease Control and Prevention. About Lipoprotein a. (2023). About Lipoprotein (a) | Heart Disease, Family Health History, and Familial Hypercholesterolemia | CDC

This publication was funded by the Kaneka Corporation.