Lp(a) in Clinical Practice: Measuring, Managing, and Mitigating Risk

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American Heart Association.

Disclaimer

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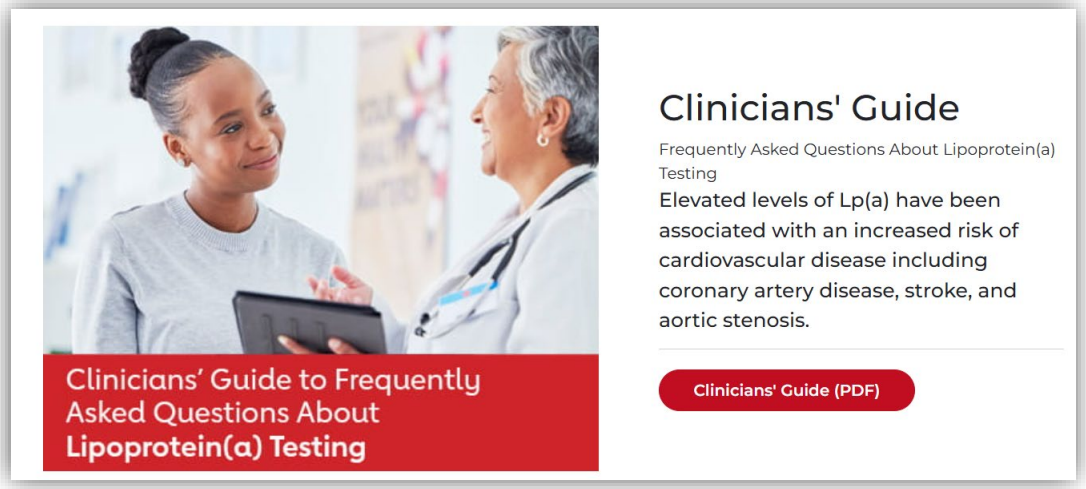
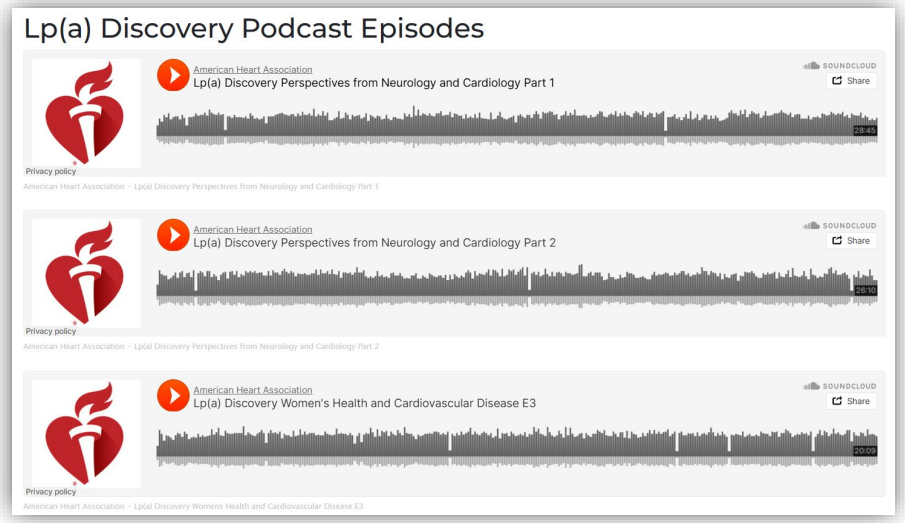
Lp(a) Discovery Project

High Lp(a) levels are a genetically inherited and are a common independent risk factor for heart disease, affecting approximately 1 in 5 people worldwide.

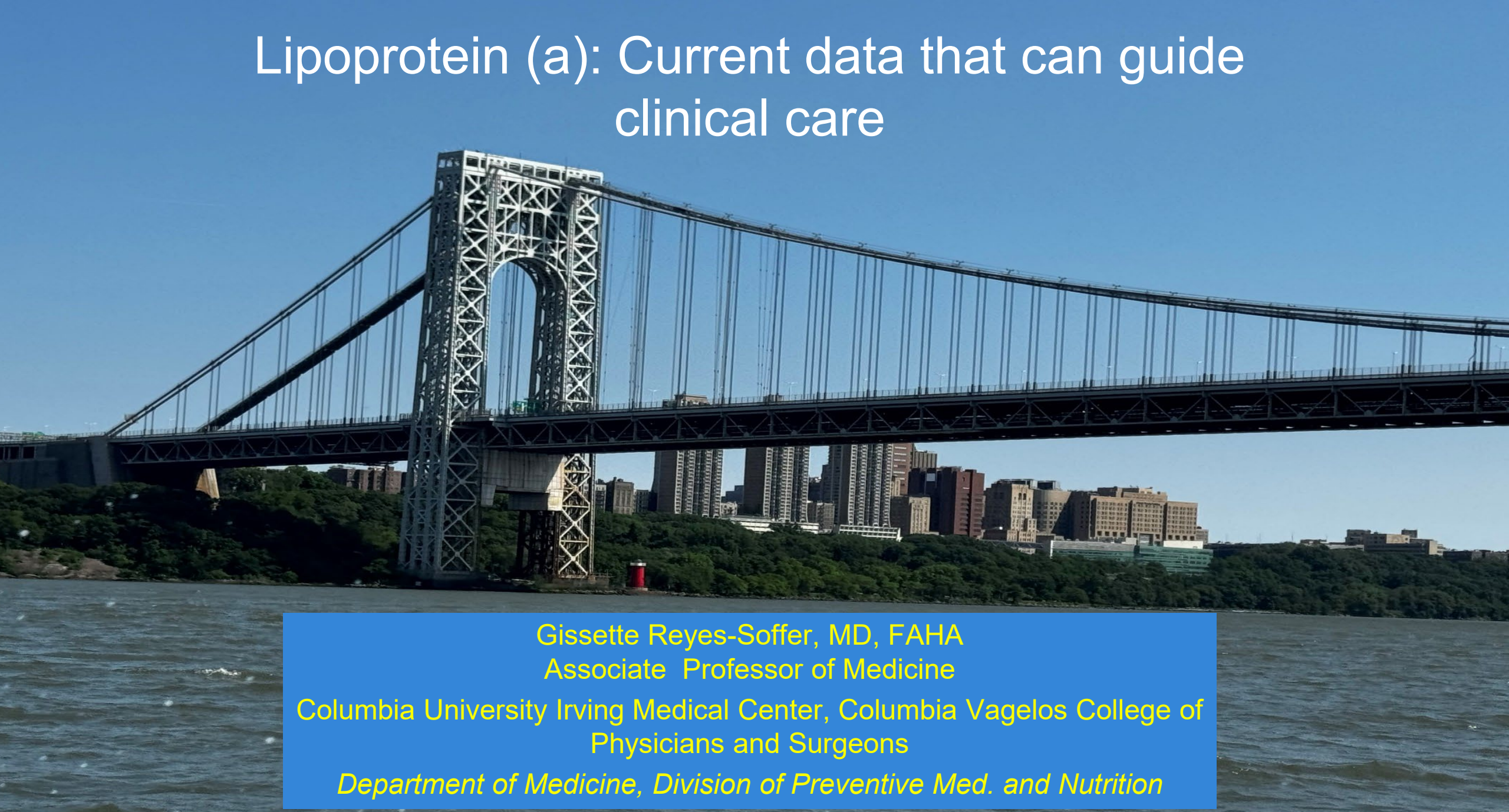
The American Heart Association (AHA) launched a 3-year national initiative, the **Lp(a) Discovery Project**, to increase Lp(a) testing by improving processes across care settings through national education.

As an enhancement to this work, the AHA launched the **Lp(a) Federally Qualified Health Center (FQHC) Discovery Project** which seeks to identify various approaches and barriers to Lp(a) testing within FQHCs and develop national education to improve knowledge and increase awareness surrounding Lp(a).





Lipoprotein (a): Current data that can guide clinical care



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Department of Medicine, Division of Preventive Med. and Nutrition

Disclosures

- R01 HL139759 (2018-2023) (2024-2028) Understanding the Complexities of Lp(a). NIH

- AHA- Innovative Project Award 2023-2025 *AHA-Innovative Project Award:23IPA1054039
  - Understanding The Metabolic Pathways of Lipoprotein(a) Through Genetic Recall

Industry

- Kaneca, Inc. Lipoprotein(a) Apharesis: Proteomics and Inflammatory Pathways

- Private Donors Funds (Robin Chemers Neustein)

Case Study: Follow up Visit

57 Y/O male
MI at 52 Y/O

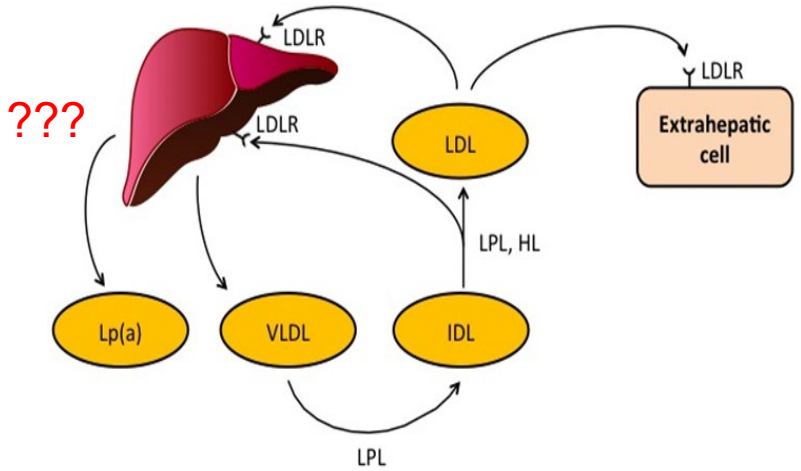
Measure: apolipoprotein B100 (apoB) and Lipoprotein (a) [apo(a)]

Triglycerides 65mg/dl
LDL-C 50mg/dl
HDL-C 40 mg/dl

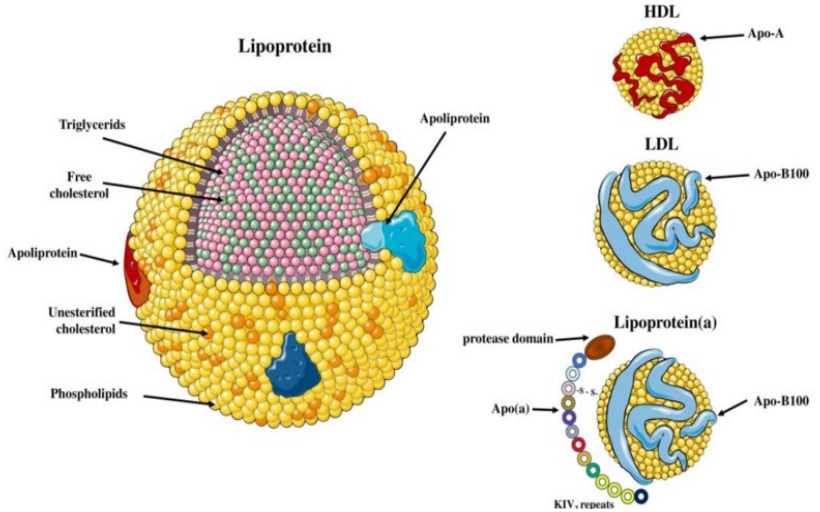
Learning Objectives

1. **Lipoproteins: Transport of Lipids and apoproteins**
2. **Why Should we Measure Lipoprotein(a)?**

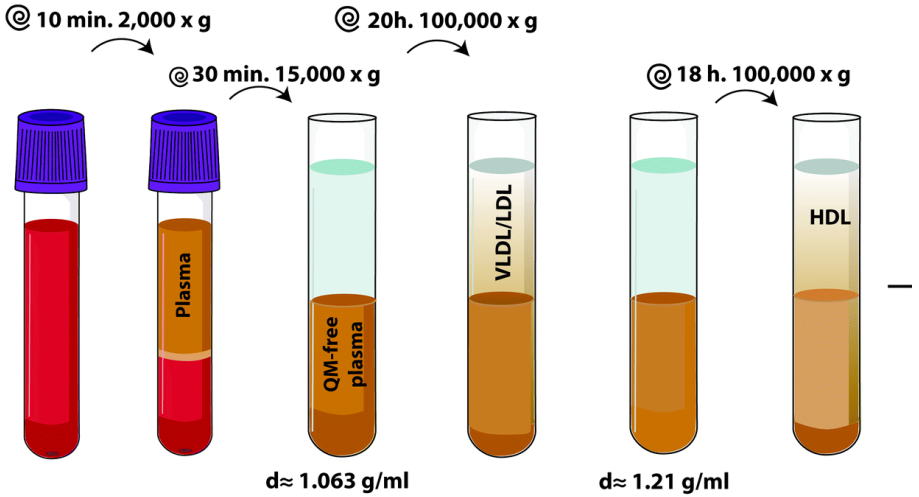
Lipoproteins: From Liver to Plasma



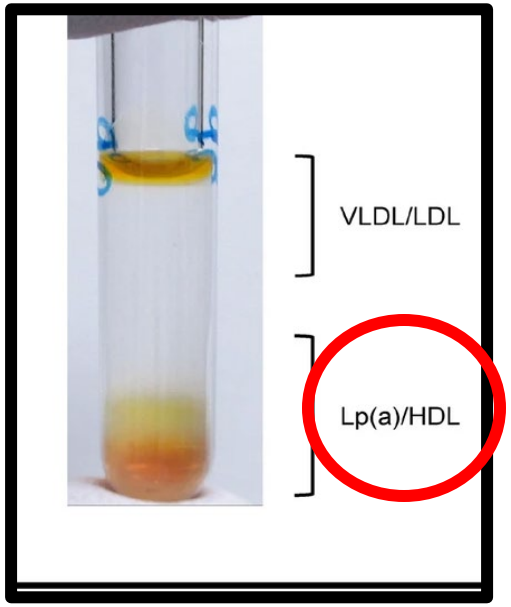
Dieplinger, B., & Dieplinger, H. (2012). New Insights into the Assembly and Metabolism of ApoB-Containing Lipoproteins from in vivo Kinetic Studies: Results on Healthy Subjects and Patients with Chronic Kidney Disease. InTech. doi: 10.5772/51865



Lampsas S, Xenou M, Oikonomou E, et al. Lipoprotein(a) in Atherosclerotic Diseases: From Pathophysiology to Diagnosis and Treatment. *Molecules*. 2023;28(3):969. Published 2023 Jan 18. doi:10.3390/molecules28030969



Uribe, K. B., Benito-Vicente, A., Martin, C., Blanco-Vaca, F., & Rotllan, N. (2021). (r)HDL in theranostics: How do we apply HDL's biology for precision medicine in atherosclerosis management? Biomaterials Science, 9(9), 3185–3208. https://doi.org/10.1039/D0BM01838D



Mueller, P. A., Yerkes, E., Bergstrom, P., Rosario, S., Hay, J., & Pamir, N. (2022). A method for lipoprotein (a) isolation from a small volume of plasma with applications for clinical research. Scientific Reports, 12, 9138. https://doi.org/10.1038/s41598-022-13040-4

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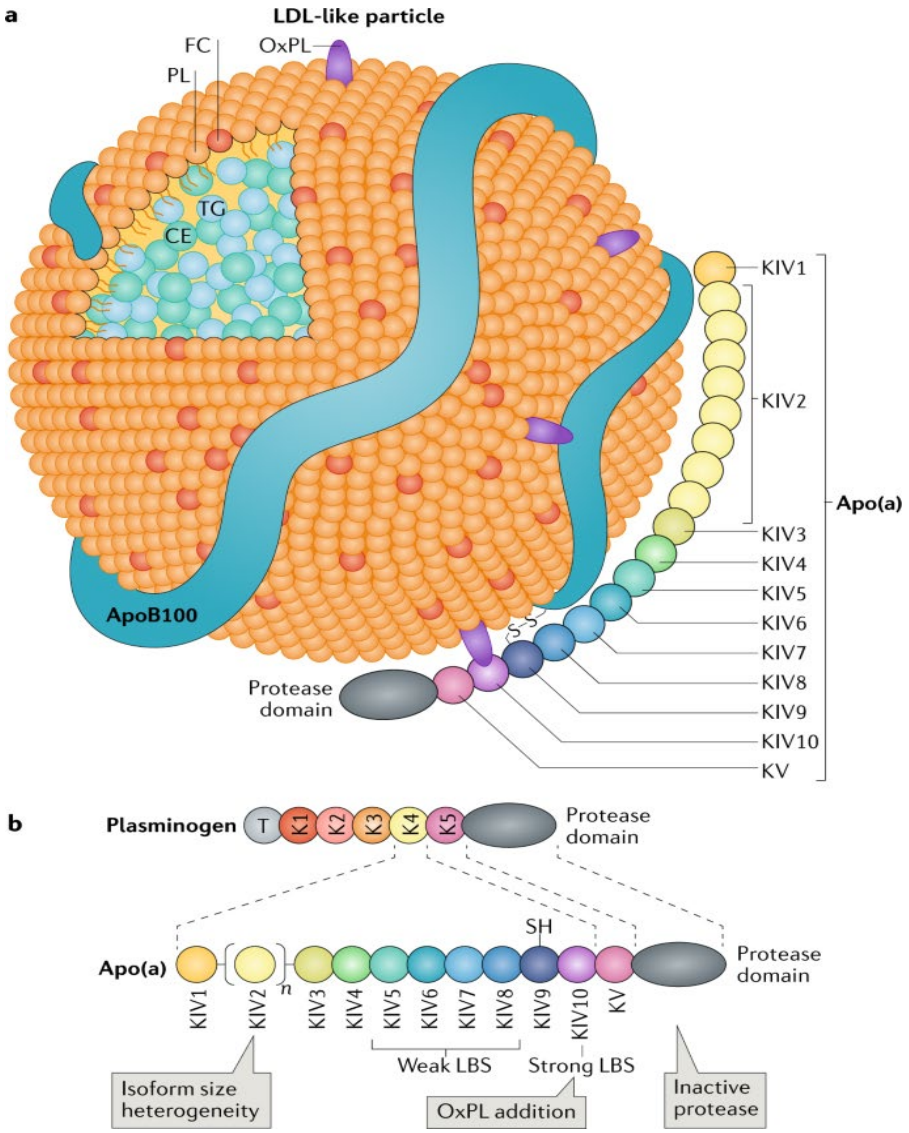
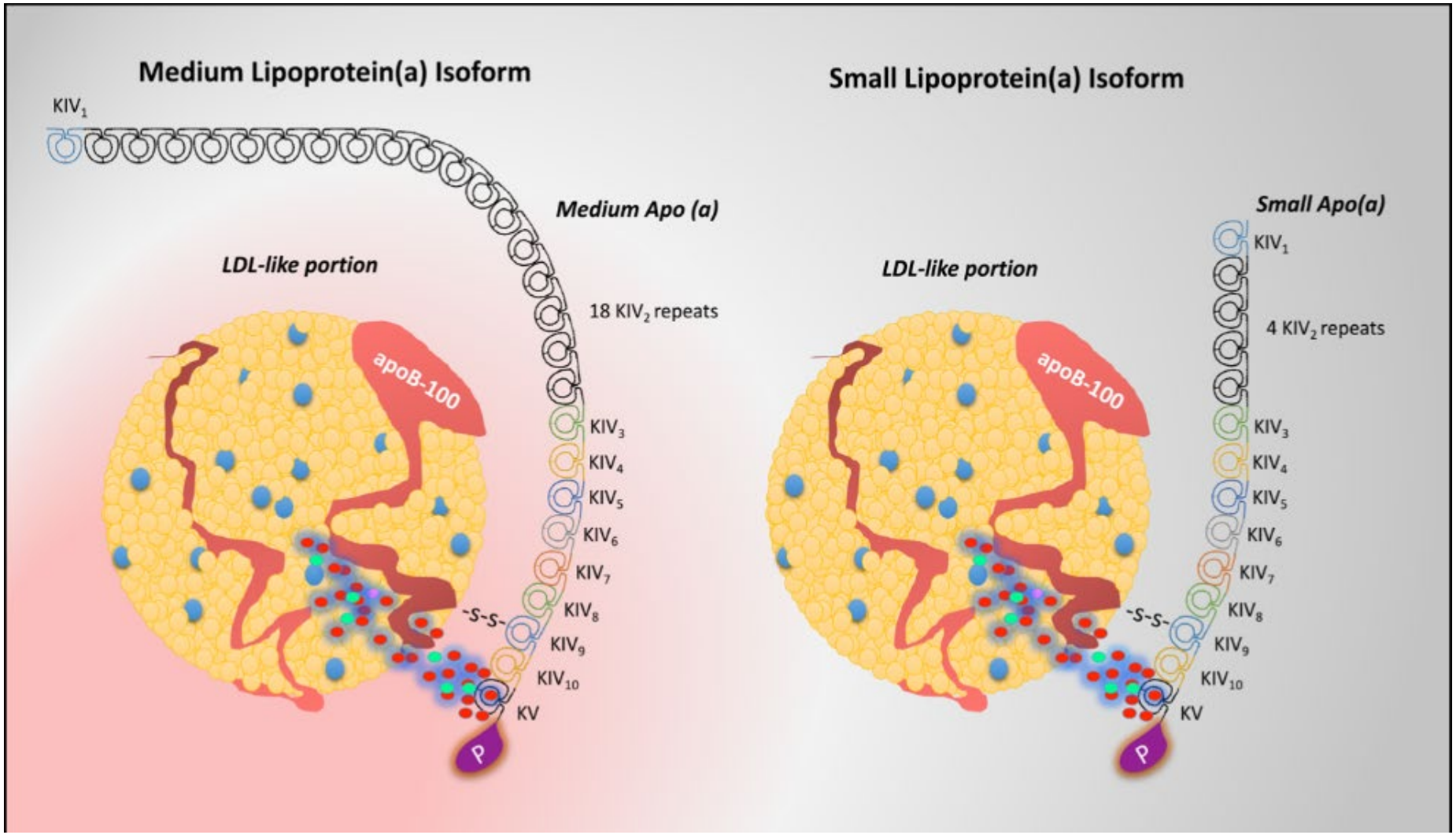
Lipoprotein(a) Particle

- ApoB100 containing Lipoprotein, covalently bound to apolipoprotein (a).
- LPA gene is one of the most potent monogenetic risk factors for CAD regardless of race and aortic stenosis
- Autosomal co-dominant inheritance, phenotype of both alleles is expressed.



Boffa MB, Koschinsky ML. Nat Rev Cardiol 2019;16:305

Lipoprotein(a) Isoforms



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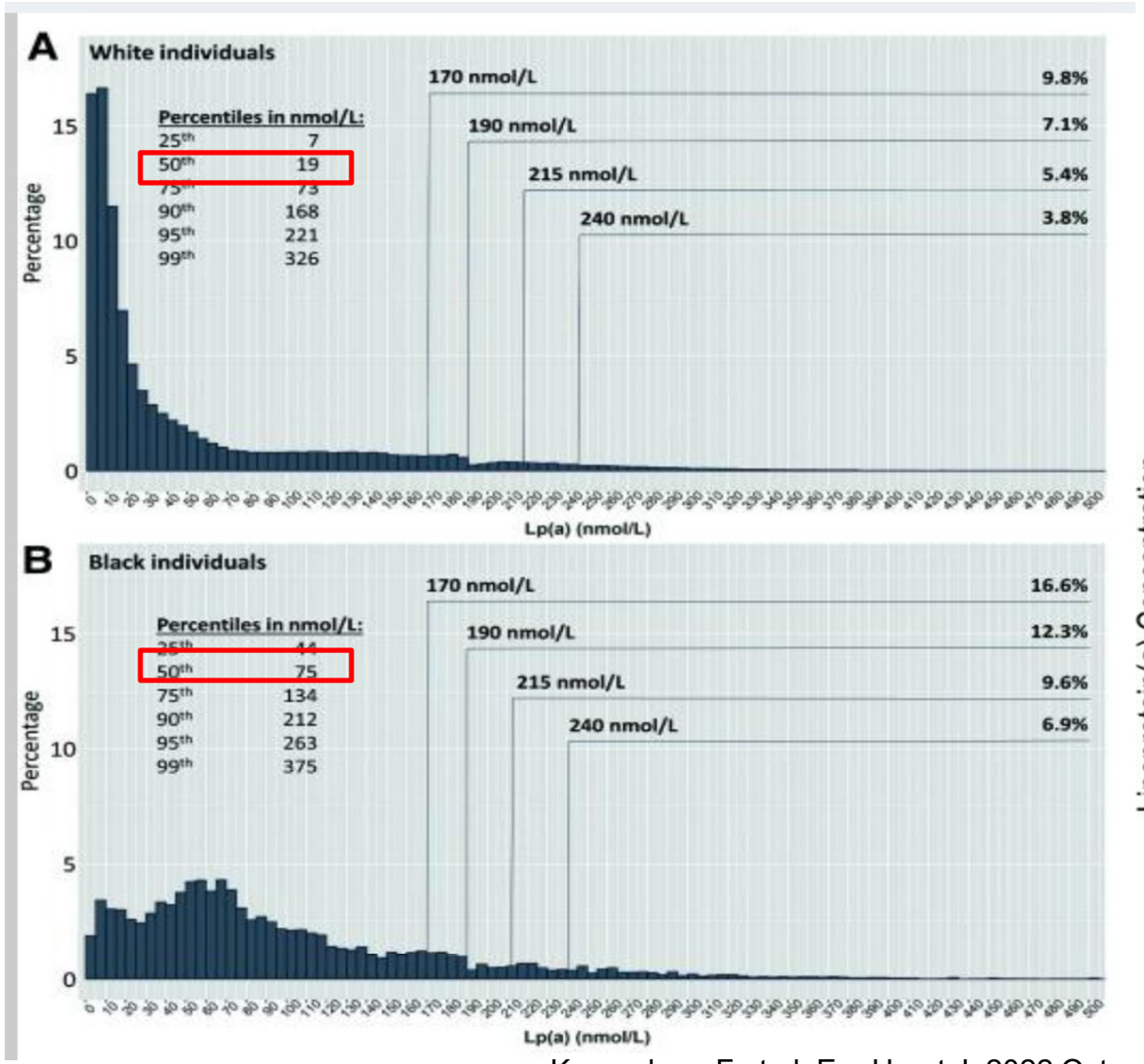
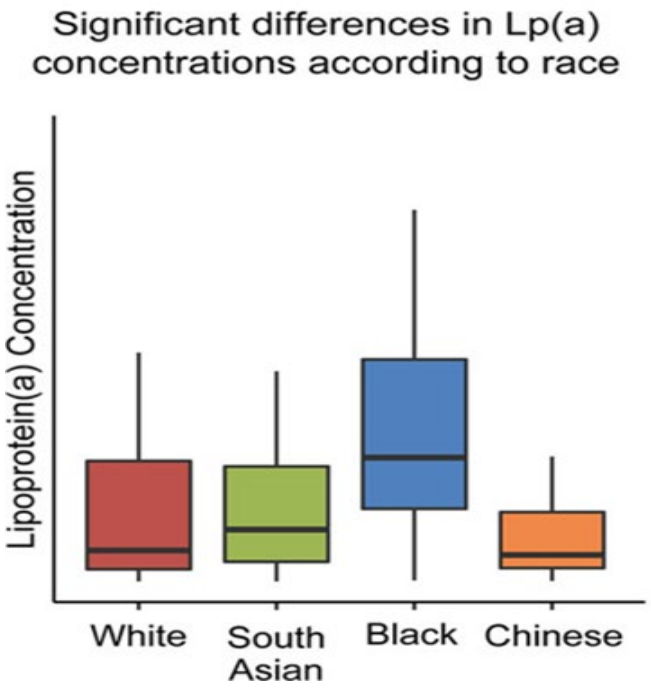
Jawi, Motasim & Frohlich, Jiri & Chan, Sammy. (2020). Lipoprotein(a) the Insurgent: A New Insight into the Structure, Function, Metabolism, Pathogenicity, and Medications Affecting Lipoprotein(a) Molecule. Journal of Lipids. 2020. 1-26. 10.1155/2020/3491764.

Lipoprotein(a) by Ancestry UK Biobank



Kronenberg F et al. Eur Heart J. 2022 Oct 14; 43(39): 3925–3946.

460,506 Adults in UK Biobank



Patel et al. Arteriosclerosis, Thrombosis, and Vascular Biology. 2021;41:465–474

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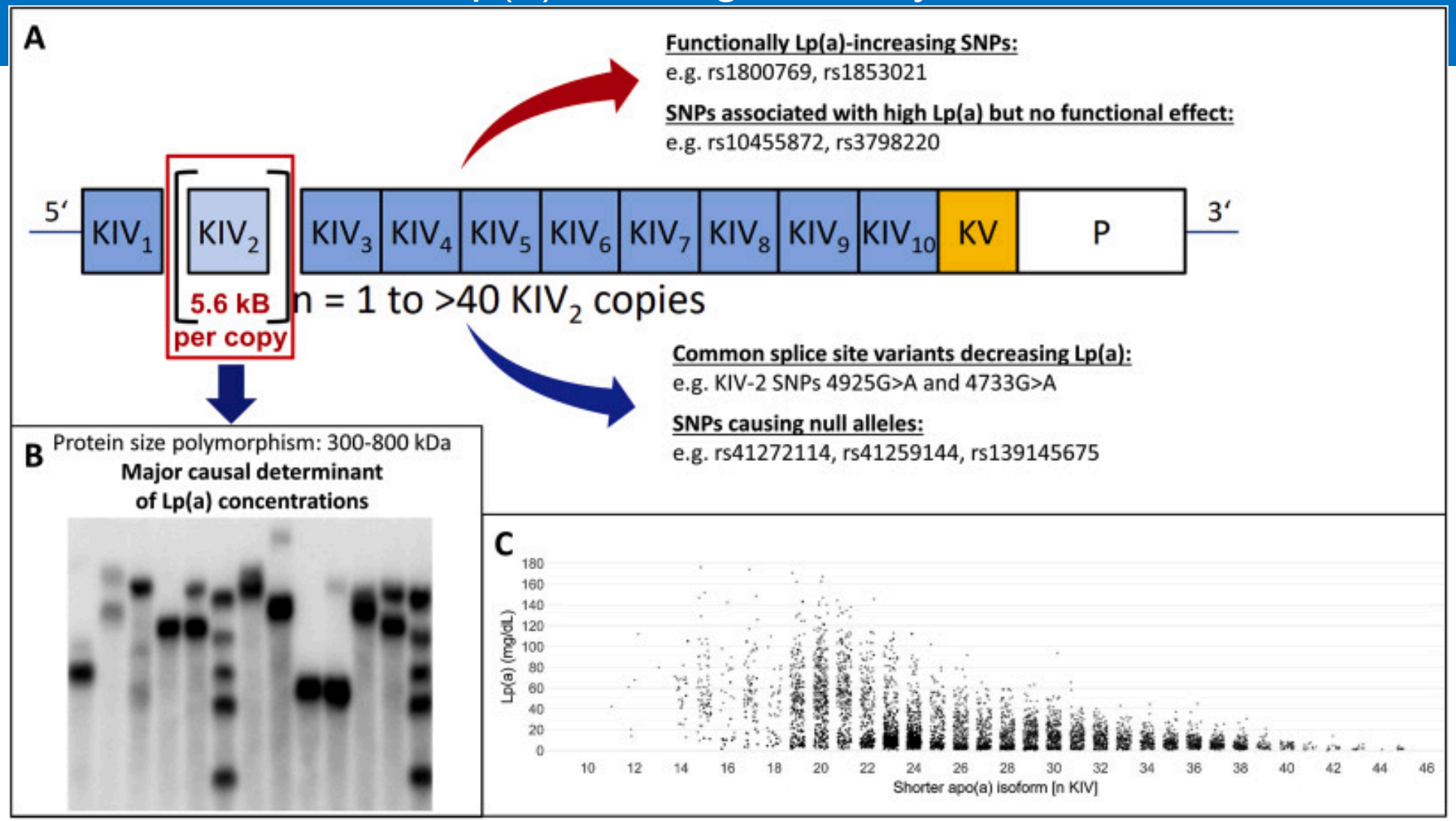
Levels of Lp(a) are Regulated by Gene Variants



Clarke R. N Engl J Med. 2009 Dec 24;361(26):2518-28.

Kronenberg F et al. Eur Heart J. 2022 Oct 14; 43(39): 3925–3946.

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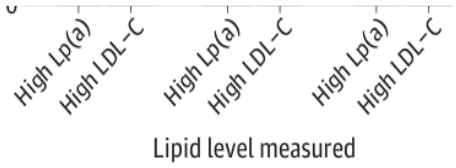
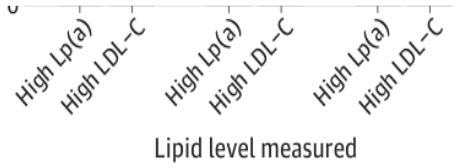
Concordance of High Lp(a) in Relatives

Figure 1. Lipoprotein(a) (Lp[a]) Levels, Concordance in High Lp(a) Levels, and Numbers Needed to Screen Among Relatives of Index Participants With High Lp(a) Levels

In this cross-sectional study, 1607 of 3420 (47.0%) first-degree relatives of UK Biobank participants with a lipoprotein(a) concentration at least 125 nmol/L were similarly affected, compared with 4974 of 30 258 (16.4%) unrelated individuals.





JAMA Cardiol. 2023 Dec 1;8(12):1111-1118.

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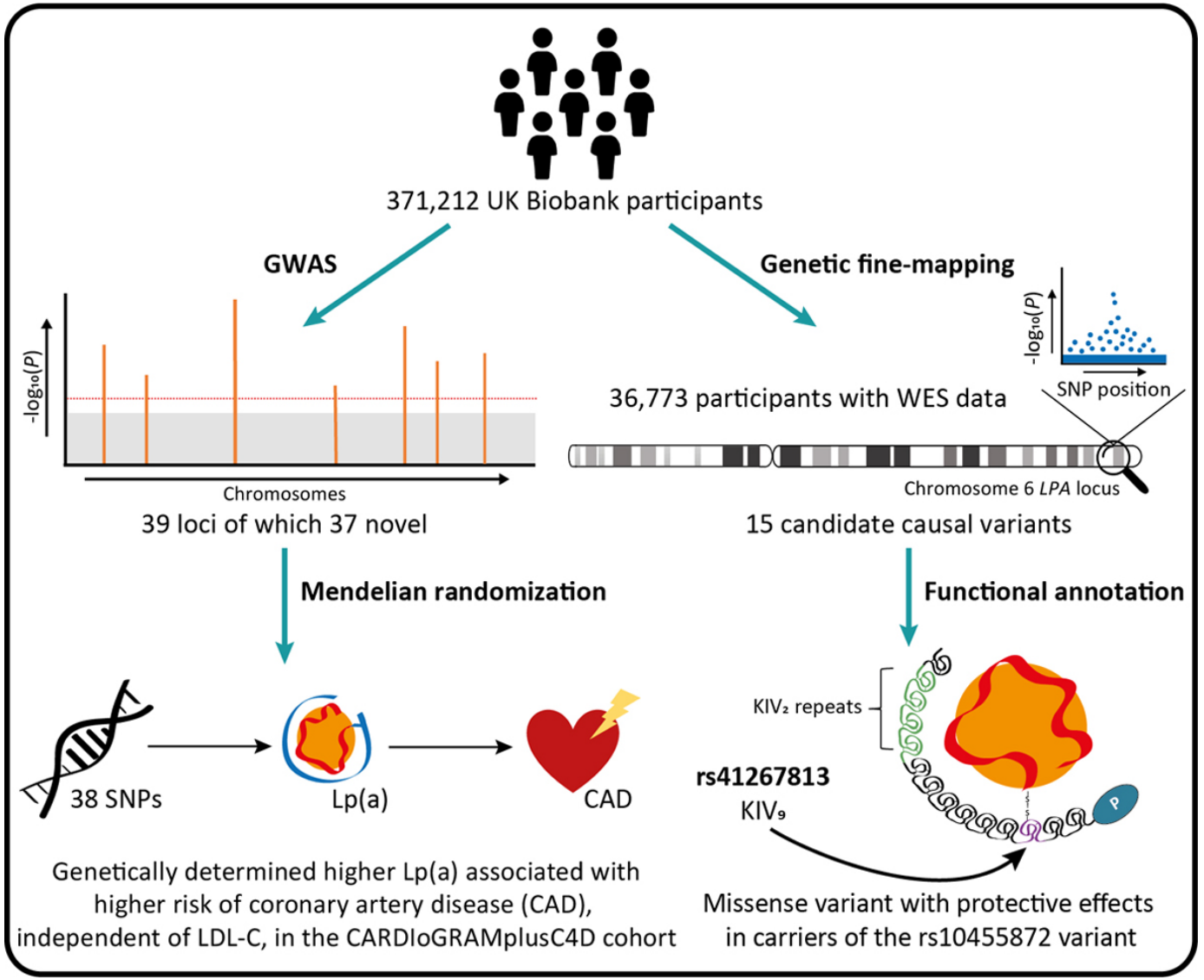
LPA Variants



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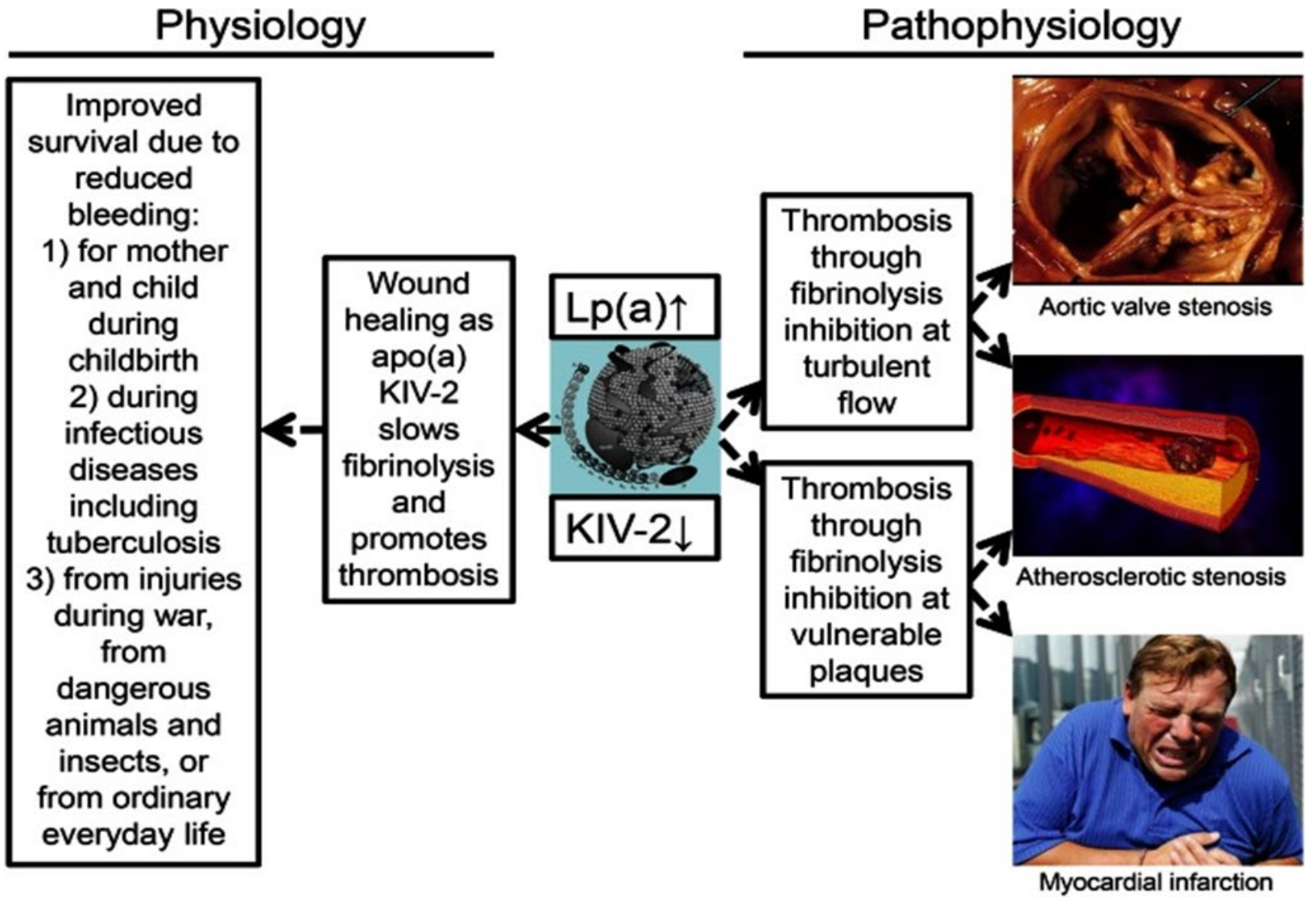
Arteriosclerosis, Thrombosis, and Vascular Biology, Volume 41, Number 5,
https://doi.org/10.1161/ATVBAHA.120.315300

Why do we have Lp(a)?



J Lipid Res. 2016 Nov; 57(11): 1953–1975.

Lp(a) and Disease

Pro-atherogenic Effects:

- Lp(a) can promote **atherosclerosis** by depositing in arterial walls.

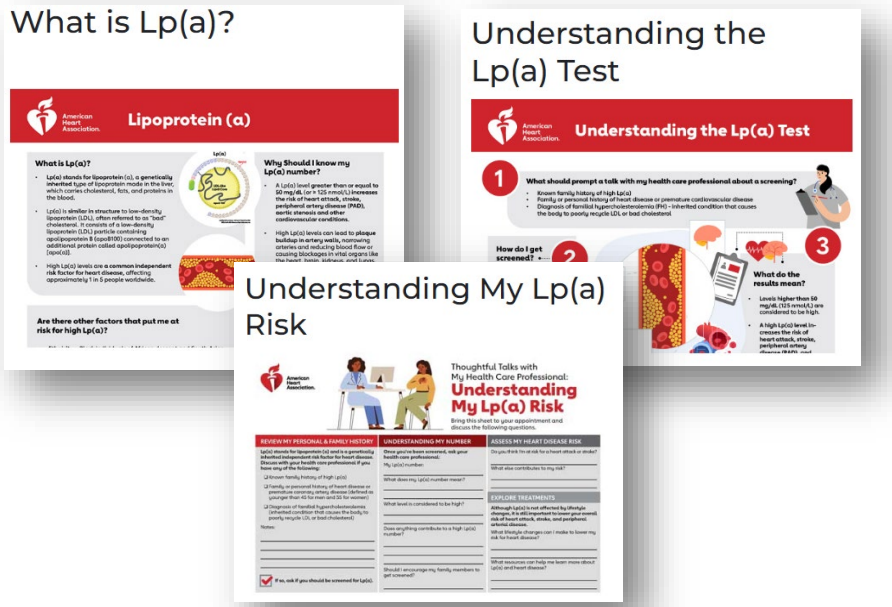
Pro-thrombotic Effects:

- Lp(a) contains **kringle IV** and **plasminogen-like** domains, which can interfere with fibrinolysis, enhancing clot formation.

Clearance and Degradation:

- Lp(a) is cleared by the liver and possibly other tissues through mechanisms involving lipoprotein receptors.

A Heart Risk Factor Even Doctors Know Little About



[Learn about Lp(a)- Patient Resources]

By Anahad O'Connor
Jan. 9, 2018, NY TIMES

E78. 41 Elevated Lipoprotein(a)
Z83. 430 Family history of elevated Lipoprotein(a)

*International Classification of Diseases, 10th Revision, Clinical Modification. https://www.cdc.gov/nchs/icd/icd10cm.htm
Engler RJM et al. *Fed Pract.* 2019;36(Suppl 7):S19-S31.

Bob Harper, the celebrity fitness trainer from the TV show "The Biggest Loser," suffered a heart attack… He eventually found out the cause was a particle in the blood called lipoprotein(a), which few doctors test for.
Hilary Swift for The New York Times

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Learning Objectives

1. Lipoproteins: Transport of Lipids and apoproteins

2. Why Should we Measure Lipoprotein(a)?

Why Measure Lp(a) – No Current targeted therapies?

- **Causality of Lp(a) in ASCVD has been established**

  Evidence Base Medicine - Research

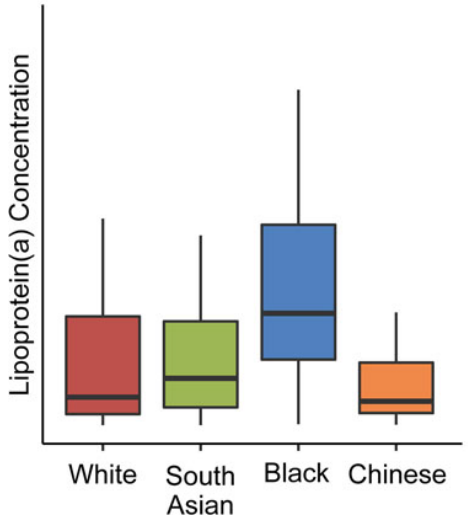
  Mendelian Randomization Studies
  Epidemiological Studies
  Clinical Studies
- **Clinical Presentations show strong associations of high Lp(a) and Low isoform size with:**

  Aortic Valve Stenosis
  Thrombosis /Peripheral Vascular Disease
  Stroke
  Myocardia Infarction

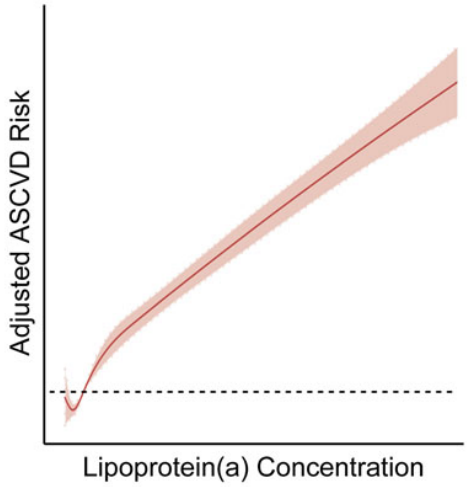
Lipoprotein(a) Increases ASCVD RISK

460,506 Adults in UK Biobank → Lipoprotein(a) Concentrations → Atherosclerotic Cardiovascular Disease

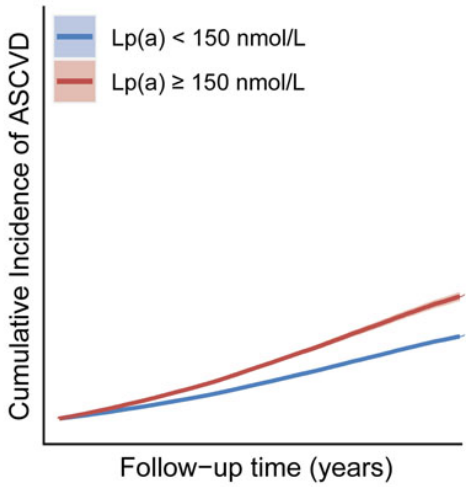
Significant differences in Lp(a) concentrations according to race



Linear rise in ASCVD risk with increasing Lp(a) concentration



Modest increase in ASCVD risk for high Lp(a) across racial groups



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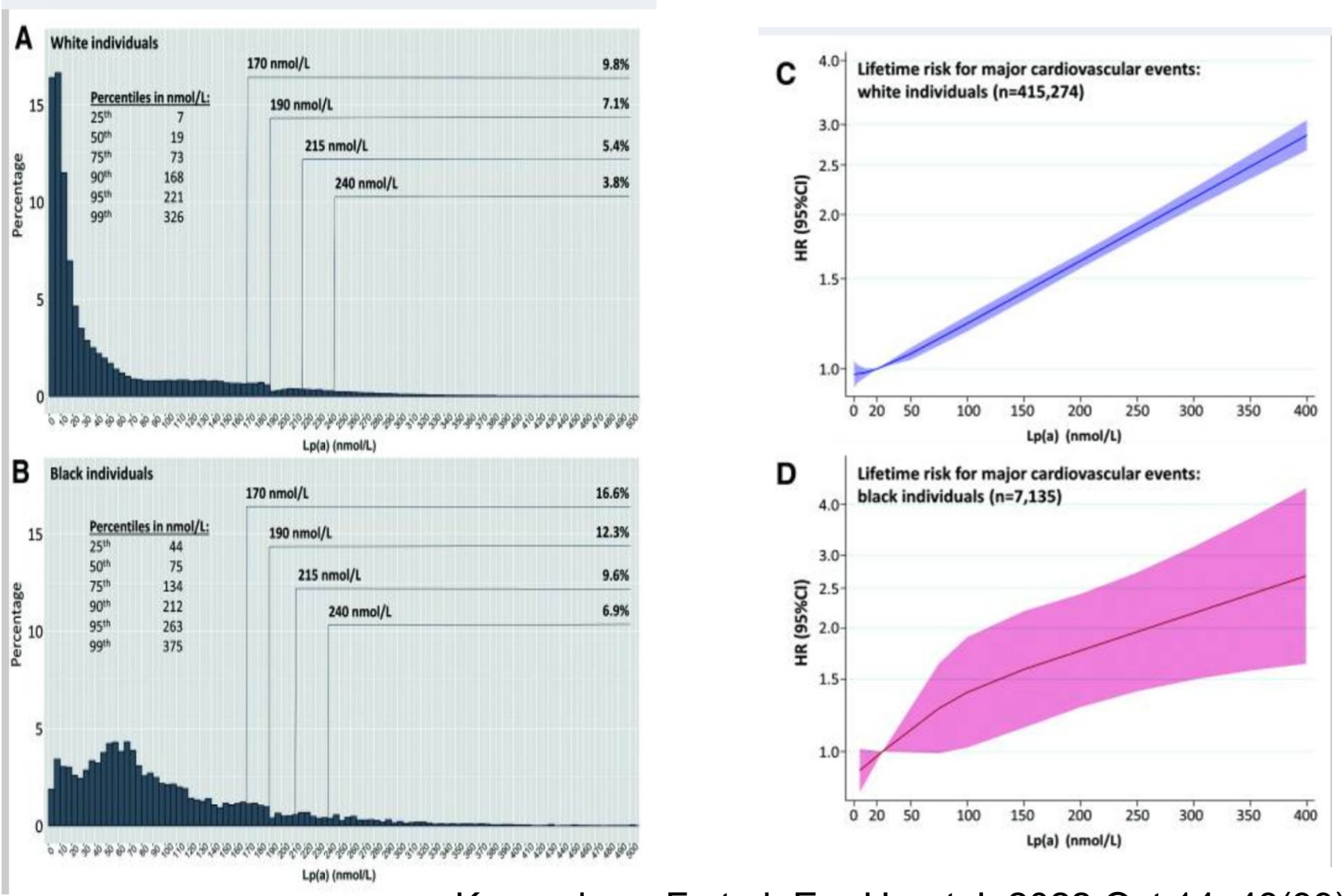
Lipoprotein(a) by Ancestry UK Biobank



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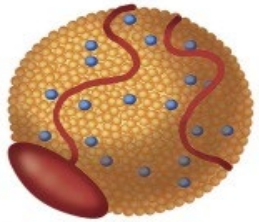
Kronenberg F et al. Eur Heart J. 2022 Oct 14; 43(39): 3925–3946.

CENTRAL ILLUSTRATION: Lipoprotein(a) and Long-Term Incidence of Atherosclerotic Cardiovascular Disease in a Multi-Ethnic Pooled Cohort in the United States



Pooled Community-Based Cohorts in the U.S. (n = 27,756)

- MESA: n = 5,892
- CARDIA: n = 4,001
- JACKSON: n = 2,098
- FHS-OS: n = 2,587
- ARIC: n = 13,178

Baseline Lp(a) (Median)	Adjusted Relative Risks (95% CI) of Incident ASCVD
<50th percentile (3.6 mg/dL) (n = 13,835)	Reference
50th-<75th percentile (13.5 mg/dL) (n = 6,960)	HR: 1.06 (95% CI: 0.99-1.14)
75th-<90th percentile (25.9 mg/dL) (n = 4,177)	HR: 1.18 (95% CI: 1.09-1.28)
≥90th percentile (52.6 mg/dL) (n = 2,784)	HR: 1.46 (95% CI: 1.33-1.59)

Mean Follow-Up 21.1 Years

Lp(a) ≥90th vs <50th Percentile

- Myocardial Infarction: HR: 1.66 (95% CI: 1.44-1.90)
- Revascularization: HR: 1.68 (95% CI: 1.48-1.91)
- Stroke: HR: 1.26 (95% CI: 1.08-1.47)
- CHD Death: HR: 1.32 (95% CI: 1.06-1.64)
- All-Cause Mortality: HR: 1.01 (95% CI: 0.93-1.08)

The relation of Lp(a) with incident ASCVD was similar by:

- Risk group (low-intermediate vs high)
- Sex (female vs male)
- Race/ethnicity (Asian, Black, Hispanic, and White)
- LDL-C category (<70, 70-<100, 100-<130, and ≥130 mg/dL)

The relation of Lp(a) (≥90th vs <50th percentile) with incident ASCVD was stronger in those with:

- Diabetes: HR: 1.92 (95% CI: 1.50-2.45) vs
- No diabetes: HR: 1.41 (95% CI: 1.28-1.55)

Overall interaction $P < 0.01$

Wong ND, et al. J Am Coll Cardiol. 2024;83(16):1511-1525.

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Is Lp(a) more atherogenic than LDL-C?

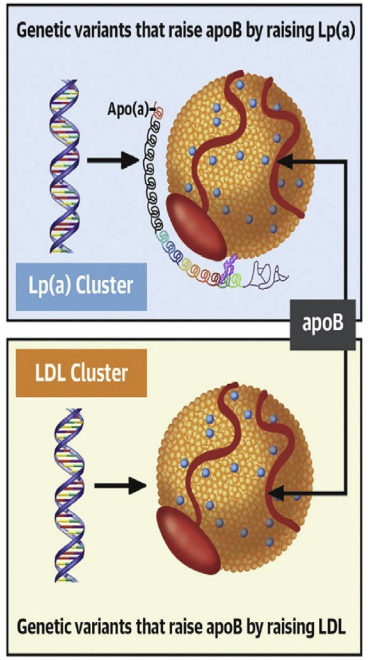
CENTRAL ILLUSTRATION: Relative Atherogenicity of Lipoprotein(a) and Low-Density Lipoprotein Particles

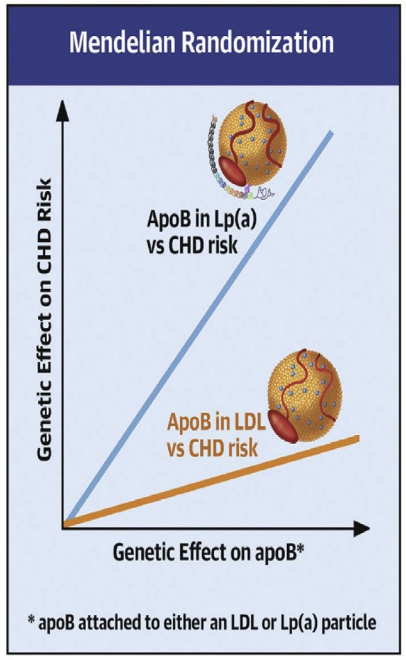
Key Question

How atherogenic is 1 particle of Lp(a) compared to 1 particle of LDL?

Key Methodology

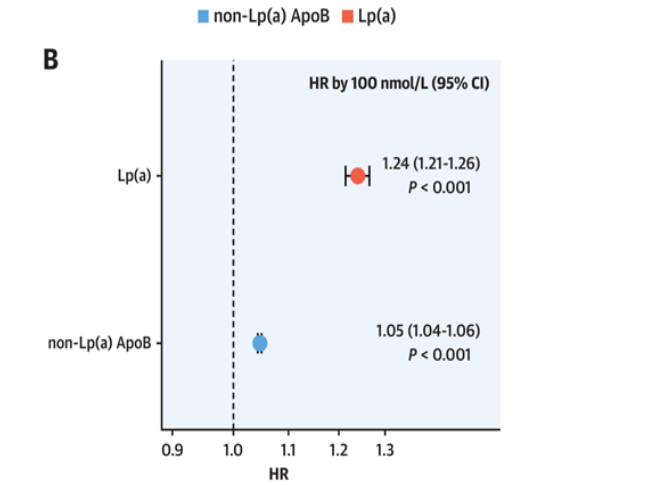
Both Lp(a) and LDL contain 1 apoB per-particle. Here, we identified genetic variants (SNPs) that affected plasma levels of either LDL particles or Lp(a) particles. For these 2 genetic SNP "clusters," we related the change in apoB to the respective change in CHD risk. This way, we directly compared the atherogenicity of LDL and Lp(a), particle for particle.





Take-Home Message: In most people, LDL particles are much more abundant than Lp(a) and carry the greatest proportion of overall CVD risk; however, on a per-particle basis, Lp(a) is about 6 times more atherogenic than LDL.

Björnson E, et al. J Am Coll Cardiol. 2024;83(3):385-395.



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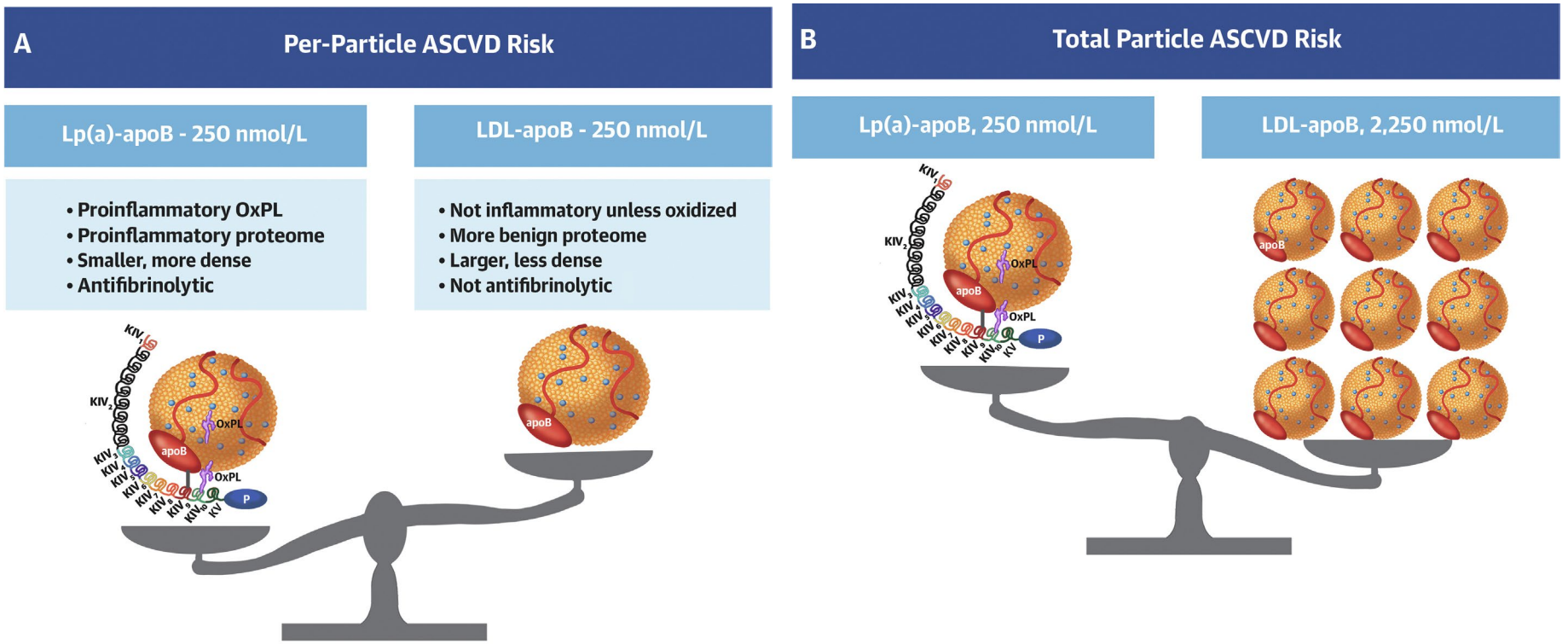
ASCVD and Lp(a)



" LDL particles are significantly more prevalent in most patients than Lp(a) particles. These observations put into clinical context the risk of ASCVD mediated by Lp(a) and LDL-C and suggest particle characteristics and particle number are both important variables in predicting ASCVD risk."

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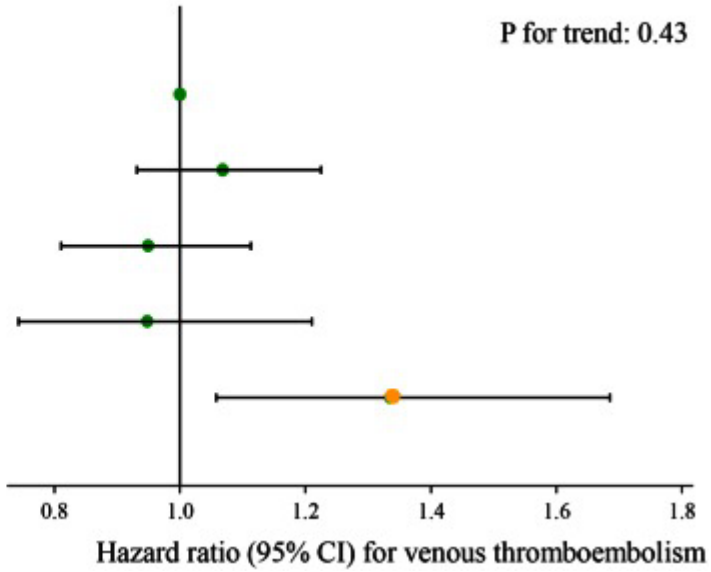
Tsimikas, S and Vera Bittner. J Am Coll Cardiol. 2024 Jan 23;83(3):396-400.

Observational associations between high plasma Lp(a) concentrations and risk of venous thromboembolism and Calcific Aortic Stenosis.

Lipoprotein(a) percentile	mg/dL	Participants events	HR(95% CI)
<22	3(2-4)	11,938/511	1.00
22-66	11(7-17)	25,756/1113	1.07(0.93;1.22)
67-89	40(30-51)	13,398/572	0.95(0.81;1.11)
90-95	80(63-95)	3398/159	0.95(0.74;1.21)
>95	124(104-148)	2816/146	1.33(1.06;1.69)



Genetic associations with **valvular calcification and aortic stenosis.** Thanassoulis G et al., CHARGE Extracoronary Calcium Working Group. N Engl J Med. 2013 Feb 7; 368(6):503-12.

European Heart Journal (2013) 34, 3268–3276
doi:10.1093/eurheartj/eht053

Controversies in cardiovascular medicine

When should we measure lipoprotein (a)?

Karam M. Kostner[1], Winfried März[2,3,4]*, and Gerhard M. Kostner[5]

Personal View *Ann Clin Biochem* 2000; **37**: 571–580

Lipoprotein(a): what's in a measure?

G Wieringa
From the Department of Biochemistry, Christie Hospital NHS Trust, Wilmslow Road, Manchester M20 4BX, UK

Lipoprotein(a) [Lp(a)] was first identified by Kare Berg in 1963 as an LDL variant.[1] domains, termed kringles (K). Apo(a) contains ten sequences that closely resemble plasmino-

Atherosclerosis 289 (2019) 181–183
Contents lists available at ScienceDirect
Atherosclerosis
journal homepage: www.elsevier.com/locate/atherosclerosis

ɔrial

challenges of measuring Lp(a): A fight against Hydra?

ıe Hydra of Lerna is a serpentine water monster in Greek my-
gy. The Hydra possessed many heads that had an enormous re-
ative capacity: whenever a head was cut off, the Hydra would
w two heads. Thus, it was not easy for the ancient hero Herakles to
gainst this constantly regenerating problem.
ıring recent decades, high serum levels of lipoprotein(a) (Lp(a))
d out to be one of the strongest genetically determined risk factors
ırdiovascular disease [1–4]. Lp(a) concentrations have been re-
d as mass of the entire particle (mass of apolipoprotein(a), apoli-

used in clinical assays are not well characterized and since almost all are polyclonal in nature almost certainly are directed against the repetitive KIV structure. This may result in a measurement bias where serum concentrations of small isoforms with a lower number of KIV_2 repeats, which are usually associated with elevated levels, are underestimated, while serum concentrations of large isoforms with a large number of KIV_2 repeats, usually associated with low levels, are overestimated (Fig. 1A). Assays having this bias are called apo(a) isoform-sensitive assays. This problem has been well recognized already a long

The Association for Clinical Biochemistry & Laboratory Medicine
Better Science, Better Testing, Better Care
Annals of Clinical Biochemistry
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DOI: 10.1177/0004563220968473
journals.sagepub.com/home/acb
SAGE

Lp(a): When and how to measure it

Jaimini Cegla[1], Michael France[2], Santica M Marcovina[3] and R Dermot G Neely[4]

Abstract
Lipoprotein(a) has long been regarded as a risk factor for cardiovascular disease; however, its routine use in clinical practice has been hampered by difficulties inherent in the measurement of this complex lipoprotein. The major challenges relate to its size heterogeneity and related issues including (1) use of appropriate calibrators (2) standardization of calibration protocols (3) traceability and (4) reporting units. In the UK, results from the current EQA schemes

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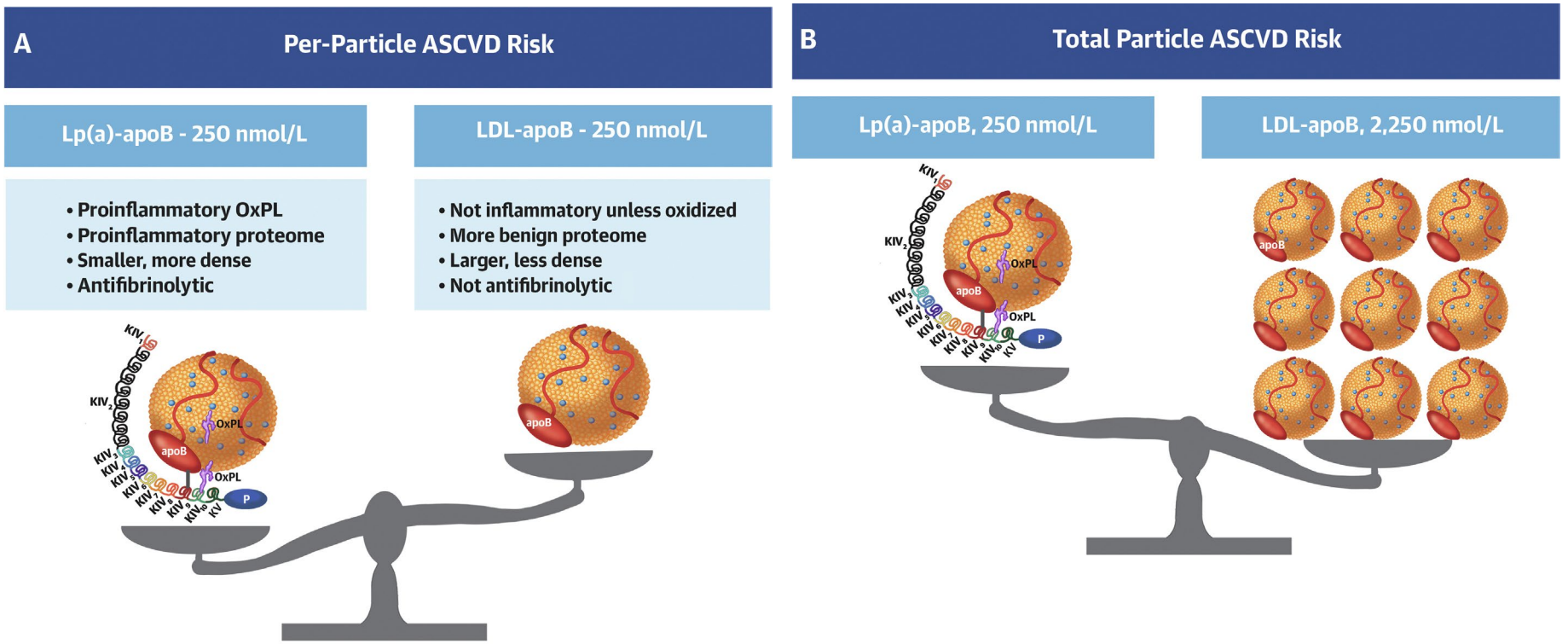
Lp(a) Measurements Mass vs. Particle Number



" LDL particles are significantly more prevalent in most patients than Lp(a) particles. These observations put into clinical context the risk of ASCVD mediated by Lp(a) and LDL-C and suggest particle characteristics and particle number are both important variables in predicting ASCVD risk."

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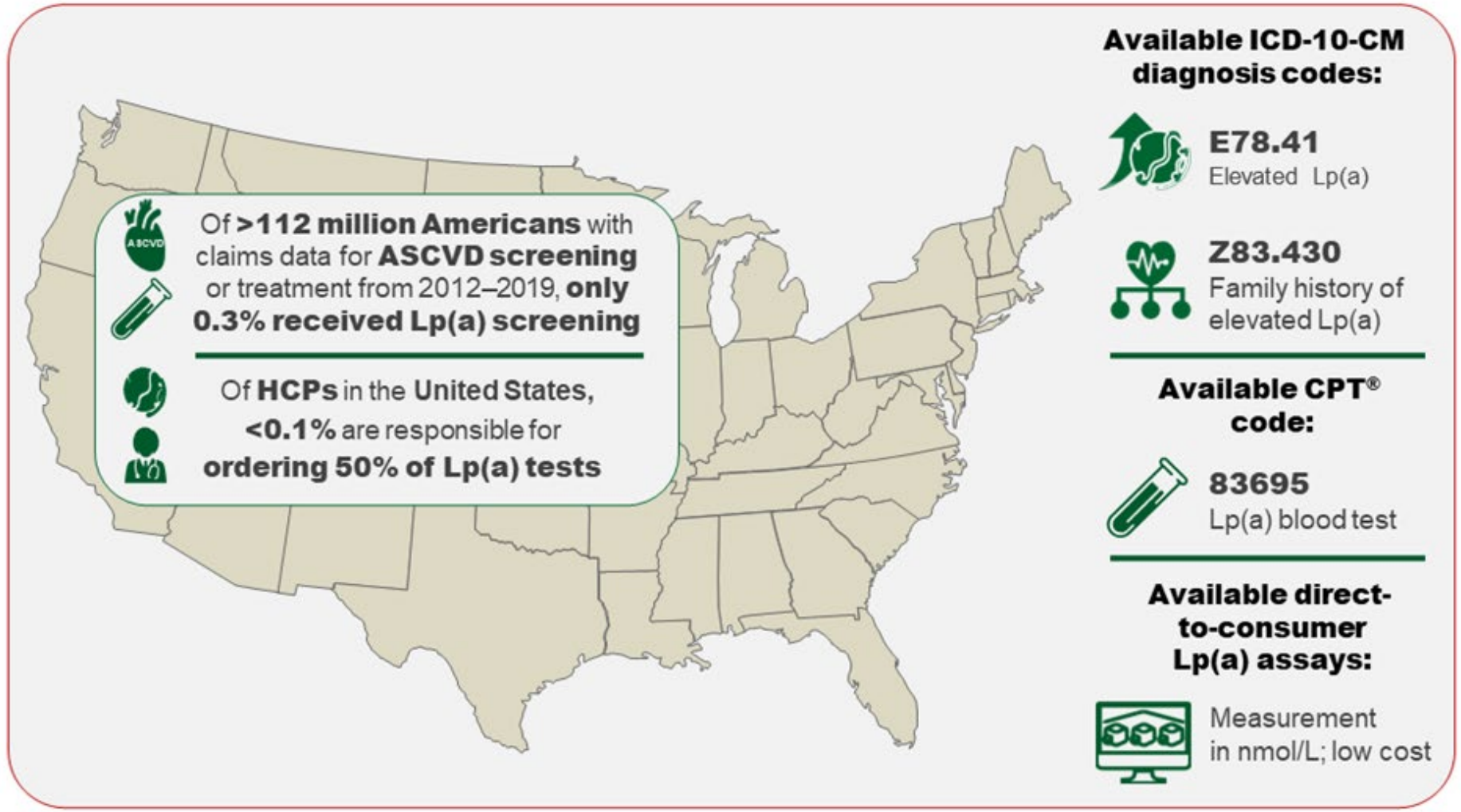
Tsimikas, S and Vera Bittner. J Am Coll Cardiol. 2024 Jan 23;83(3):396-400.



Am J Prev Cardiol. 2024 Apr 3:18:100651

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When Do We Measure Lp(a)

Am J Prev Cardiol. 2024 Apr 3:18:100651

Are we measuring Lp(a)?

Marianna Pavlyha, MD 0-PGY4 UCLA Vascular Surgery

Yihao Li, Data Scientist

N=56,833 4% (2,249)

0.3% tested in general population
73% of patients compliant with test

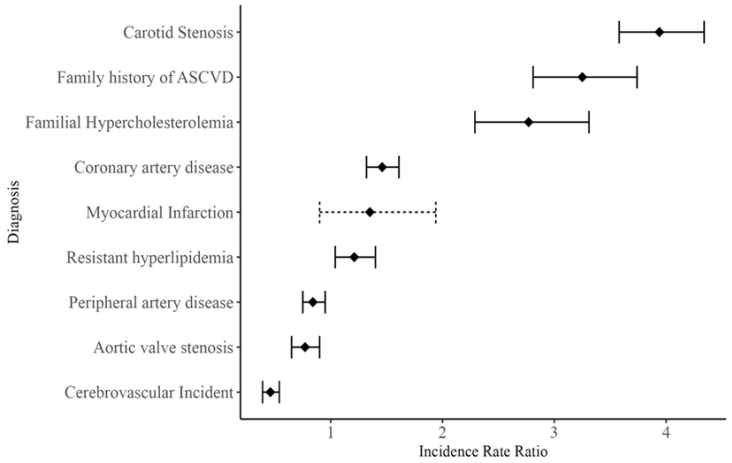
SRRE

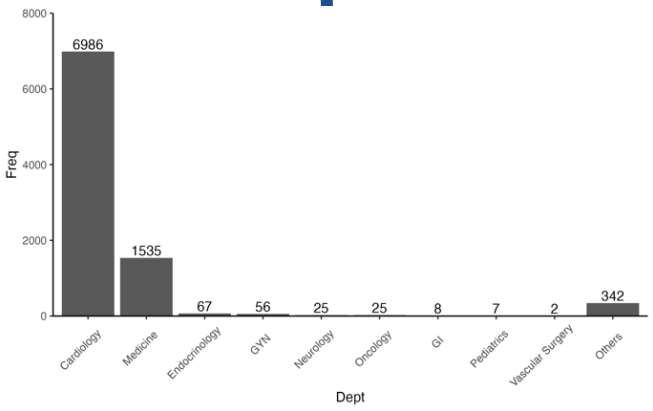
SRRE	RR	P-value
Black	0.39	<0.001***
Hispanic	0.35	<0.001***
Others/ Unknown	0.82	<0.001***
White		

Environment/ Socioeconomic score (SES)

SES	RR	P-value
SES 1 low		
SES 2	0.54	<0.001***
SES 3 high	0.63	<0.001***

Diagnosis





Ordering Providers

Personal Income/ Insurance

Medicaid vs no Medicaid

SRRE	RR	P-value
No Medicaid		
Medicaid	0.65	<0.001***

Pavlyha M et al. J Clin Lipidol. 2024 Sep-Oct;18(5):e720-e728.

Arteriosclerosis, Thrombosis, and Vascular Biology
Volume 42, Issue 1, January 2022; Pages e48-e60
https://doi.org/10.1161/ATV.0000000000000147

AHA SCIENTIFIC STATEMENT

Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease: A Scientific Statement From the American Heart Association

Gissette Reyes-Soffer, MD, FAHA, Chair, Henry N. Ginsberg, MD, FAHA, Lars Berglund, MD, PhD, P. Barton Duell, MD, FAHA, Sean P. Heffron, MD, MS, MSc, Pia R. Kamstrup, MD, PhD, Donald M. Lloyd-Jones, MD, ScM, FAHA, Santica M. Marcovina, PhD, ScD, FAHA, Calvin Yeang, MD, PhD, and M
Heart Association Coun
Cardiovascular Radiolo

ESC European Society of Cardiology
European Heart Journal (2022) 43, 3925–3946
https://doi.org/10.1093/eurheartj/ehac361

SPECIAL ARTICLE
Miscellaneous

Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement

Florian Kronenberg [1], Samia Mora [2], Erik S.G. Stroes [3], Brian A. Ference[4], Benoit J. Arsenault [5], Lars Berglund[6], Marc R. Dweck [7], Marlys Koschinsky [8], Gilles Lambert [9], François Mach[10], Catherine J. McNeal [11], Patrick M. Moriarty[12], Pradeep Natarajan [13], Børge G. Nordestgaard [14,15], Klaus G. Parhofer [16], Salim S. Virani [17], Arnold von Eckardstein [18], Gerald F. Watts[19], Jane K. Stock[20], Kausik K. Ray[21], Lale S. Tokgözoğlu[22], and Alberico L. Catapano [23,24]

ARTICLE IN PRESS
JID: JACL [mNS;March 29, 2024;17:27]
Journal of Clinical Lipidology (2024) 000, 1–12
Journal of Clinical Lipidology

A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice

Marlys L. Koschinsky, PhD, Archna Bajaj, MD, MSCE, Michael B. Boffa, PhD, Dave L. Dixon, PharmD, Keith C. Ferdinand, MD, Samuel S. Gidding, MD, Edward A. Gill, MD, Terry A. Jacobson, MD, Erin D. Michos, MD, MHS, Maya S. Safarova, MD, PhD, Daniel E. Soffer, MD, Pam R. Taub, MD, Michael J. Wilkinson, MD, Don P. Wilson, MD, Christie M. Ballantyne, MD*

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Case Study: Follow up Visit

57 Y/O male
MI at 52 Y/O
current symptom: SOB, chest pain, lower extremity pain.
Currently on:
Statins, Ezetemibe, PCKS9 Inh
Total Chol 150mg/dl
Triglycerides 65mg/dl
LDL-C 50mg/dl
HDL-C 40 mg/dl
Please add apoB, Lp(a)?

Internal and External Teams and Collaborators

- **Research Participants**
- **Lab Members (Current)**
  - Lab Tech: Nelsa Matienzo (BA)
  - Staff Scientist Anastasiya Matveyenko (BA, MS, MS) *
  - T32-Post-Doc Marianna Pavlyha, MD (UCLA vascular surgery PGY-4)
  - Nurse Practitioner: Lau Y. Yung, NP (Cindy)
  - Modeling/Statistics Team: Tiffany Thomas PhD/ Rajasekhar Ramakrishnan ScD
  - Data Scientist Yihao Li, BS
- CUIMC Collaborators
  - Henry Ginsberg and Laboratory **Neurology**: Badri Vardajeran

Other Collaborators Santica Marcovina- Medpace

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Prevention of ASCVD in the Setting of Elevated Lp(a): 2025 and Beyond

Donald M. Lloyd-Jones, FAHA FACC FASPC
Alexander Graham Bell Professor of Medicine
Director, Framingham Center for Population & Prevention Science
PI, Framingham Heart Study
Section Chief of Preventive Medicine & Epidemiology
Boston University Chobanian & Avedisian School of Medicine
Past President, American Heart Association

Disclosures

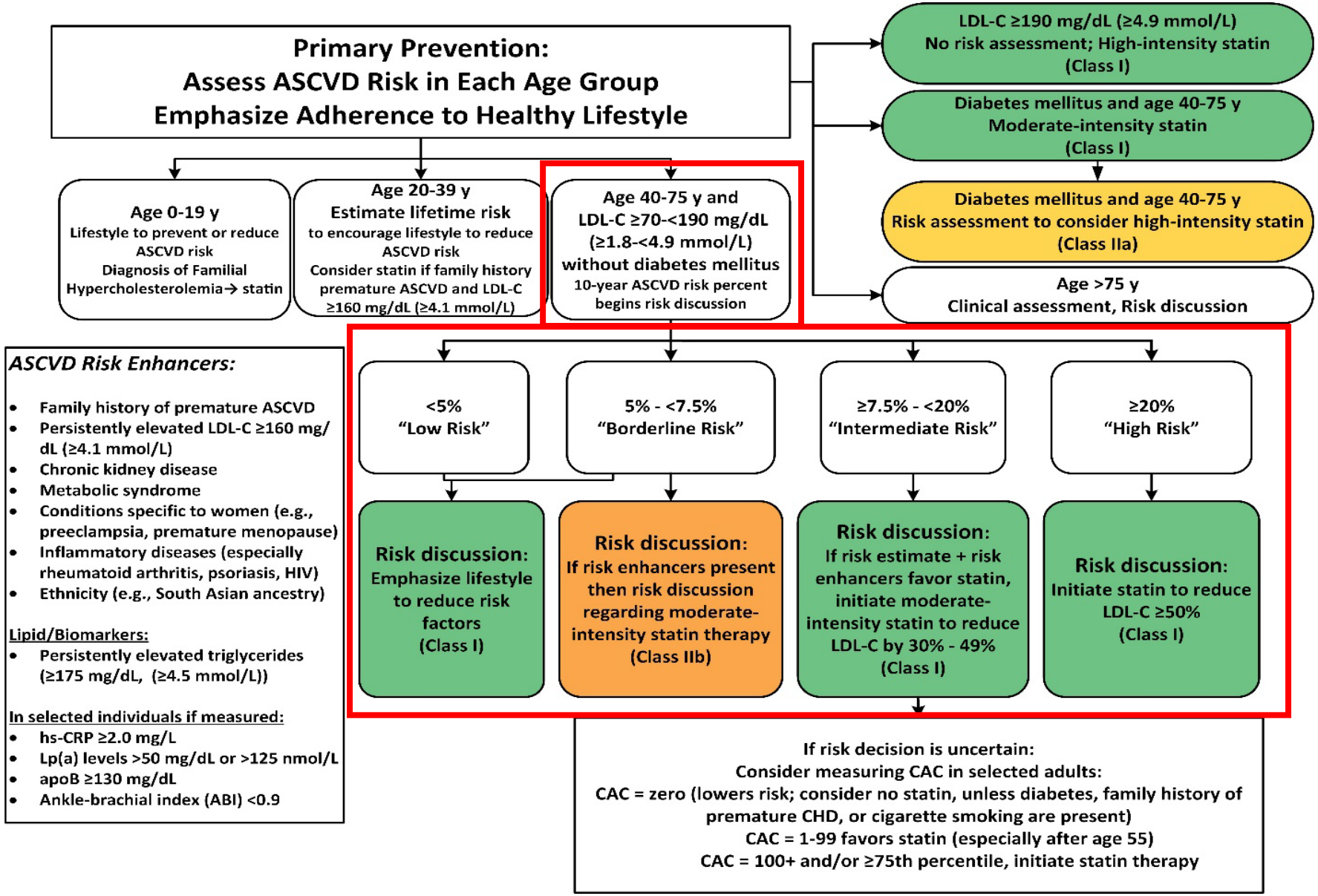
- Dr. Lloyd-Jones has no relationships with industry/conflicts of interest
  - Grant funding: NIH, CMS, AHA
- Dr. Lloyd-Jones serves as an unpaid fiduciary director of the American Heart Association

Outline and Objectives

- Context of risk
- Current prevention strategies
  - Lifestyle
  - LDL-C (and ApoB!) lowering
  - NOT niacin or estrogen
- Future prevention strategies?
  - Direct Lp(a) inhibition (stay tuned)

Context of Underlying Risk

2018 AHA/ACC/Multi-Specialty Cholesterol Guidelines



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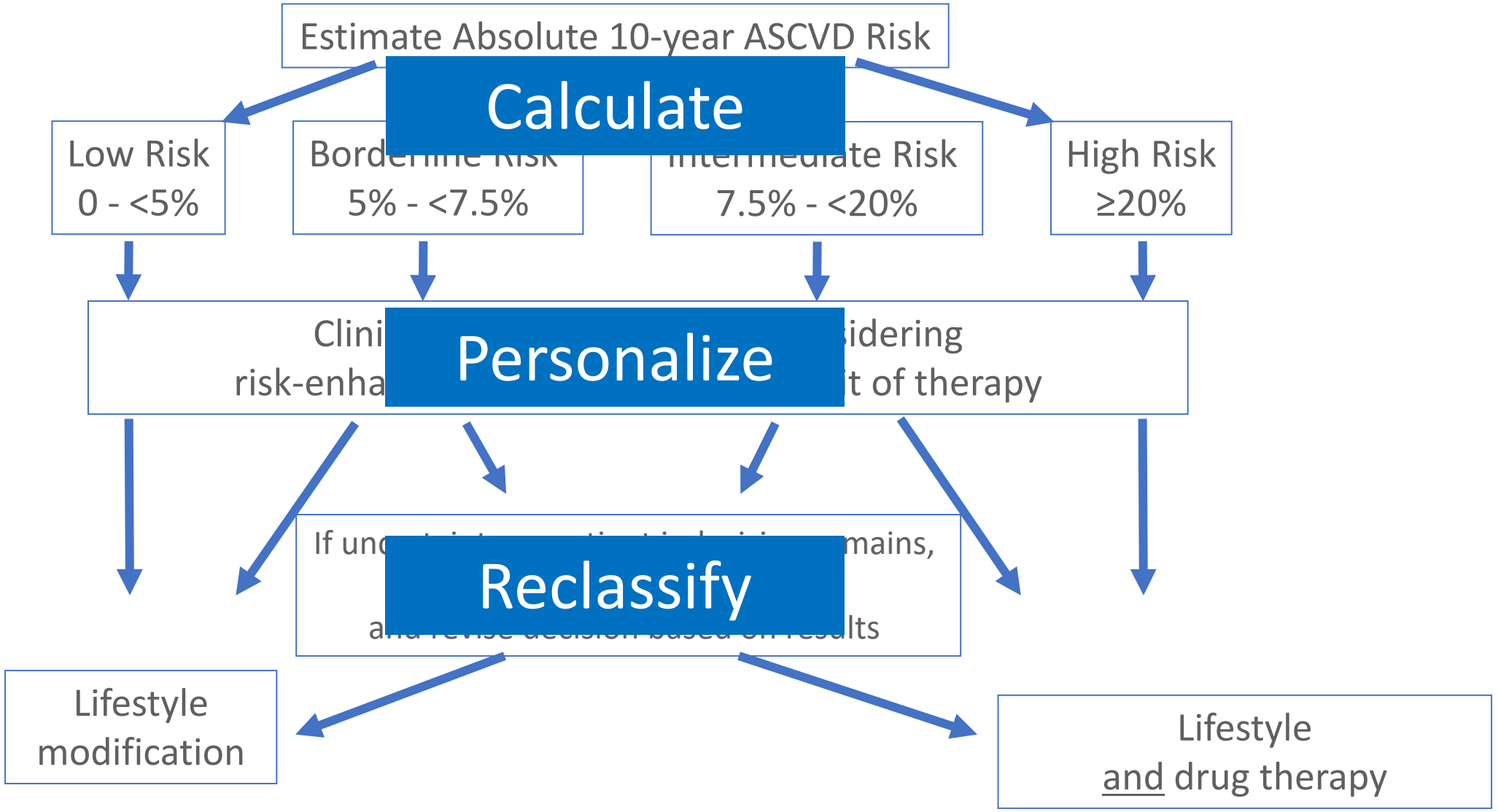
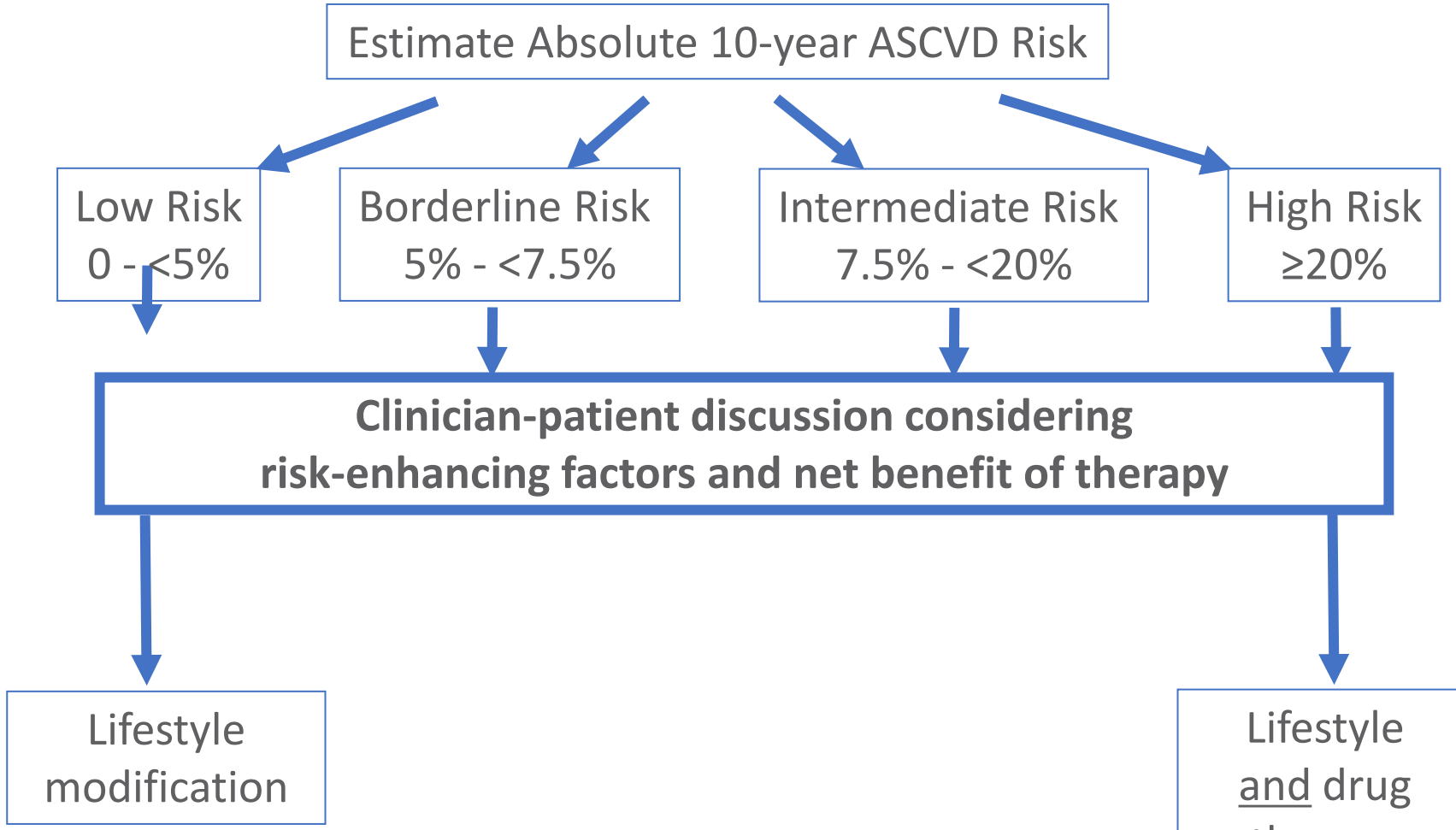
Approach to Risk Assessment in 1° Prevention



C = Calculate: Tools for Risk Estimation

- Pooled Cohort Equations – App or Online (or EHR programmable)
- ACC ASCVD Risk Estimator Plus (online/app)
  - http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/
- AHA ASCVD Risk Calculator (online/app)
  - http://static.heart.org/riskcalc/app/index.html#!/baseline-risk

P = Personalize: Refine Risk for Individual Patients



P = Personalize: Refine Risk for Individual Patients

Risk-Enhancing Factors

- Family hx of premature ASCVD
- 1º hypercholesterolemia (LDL-C 160-189 mg/dL)
- Metabolic syndrome
- Chronic kidney disease
- Chronic inflammatory conditions (RA, psoriasis, HIV)
- Hx premature menopause or pregnancy-associated risk conditions
- High-risk race/ethnic groups
- Lipid/biomarkers
  - 1º hypertriglyceridemia
  - If measured:
    - Elevated hs-CRP ≥2 mg/L
    - Elevated Lp(a) ≥50 mg/dL
    - Elevated apoB ≥130 mg/dL
    - ABI <0.9

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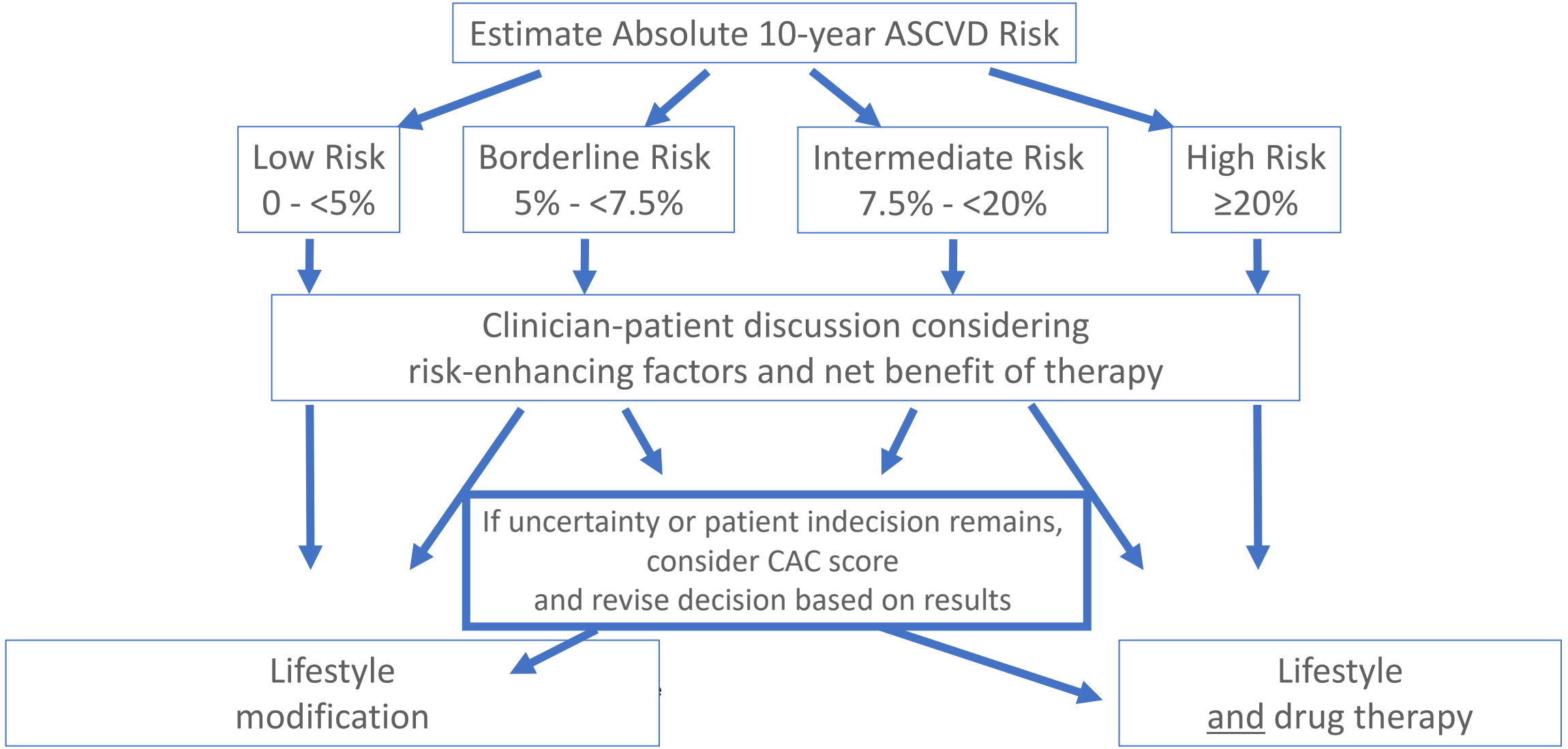
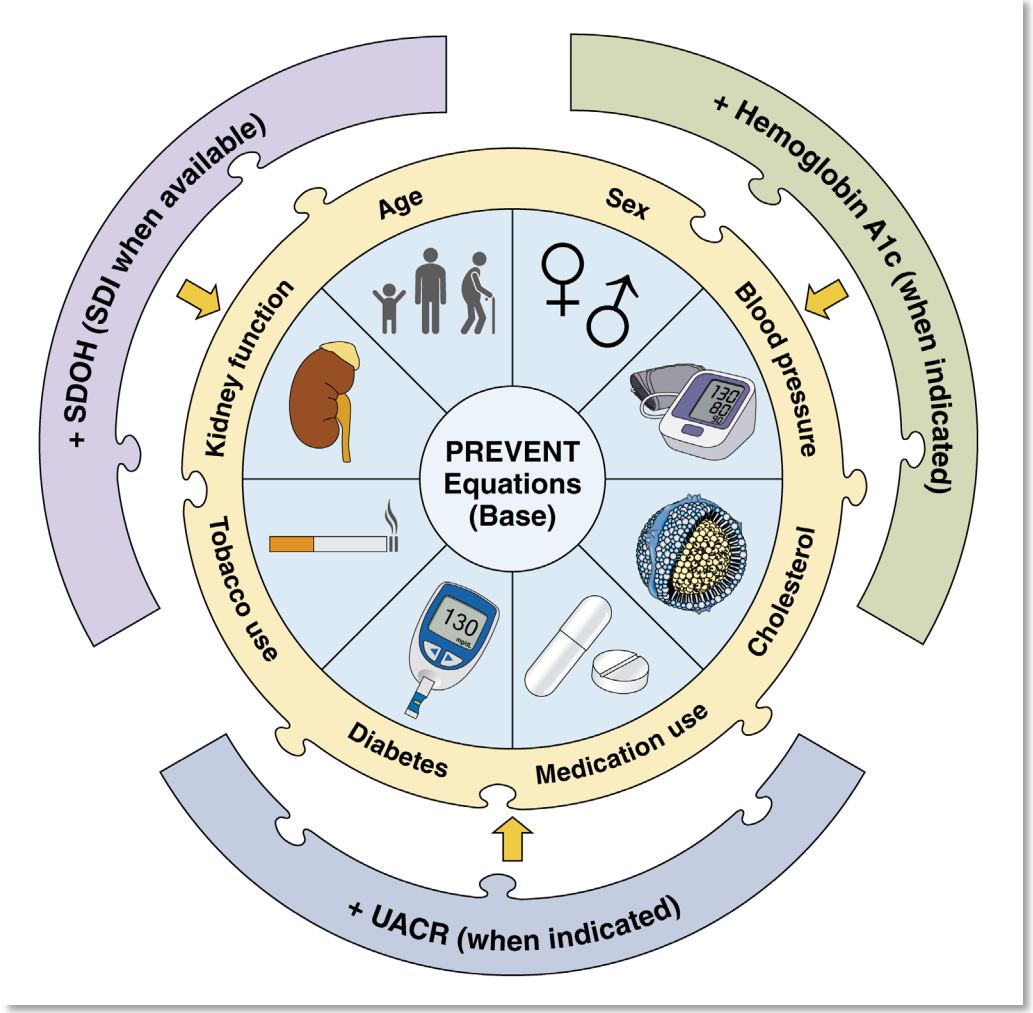
R = Reclassify Risk in Selected Patients



New paradigm for CVD risk: PREVENT™



Predictors:

- Base: Traditional risk factors (SBP, non-HDL cholesterol, diabetes, anti-hypertensive, lipid-lowering, smoking,) plus eGFR, BMI
- Add-on (if known): UACR, HbA1c, SDI

Abbreviations: CVD indicates cardiovascular disease; PREVENT, Predicting Risk of CVD Events; SDI, social deprivation index; SDOH, social determinants of health; and UACR urine albumin-to-creatinine ratio.

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Khan SS et. al. *Circulation* 2023

New paradigm for CVD risk: PREVENT™

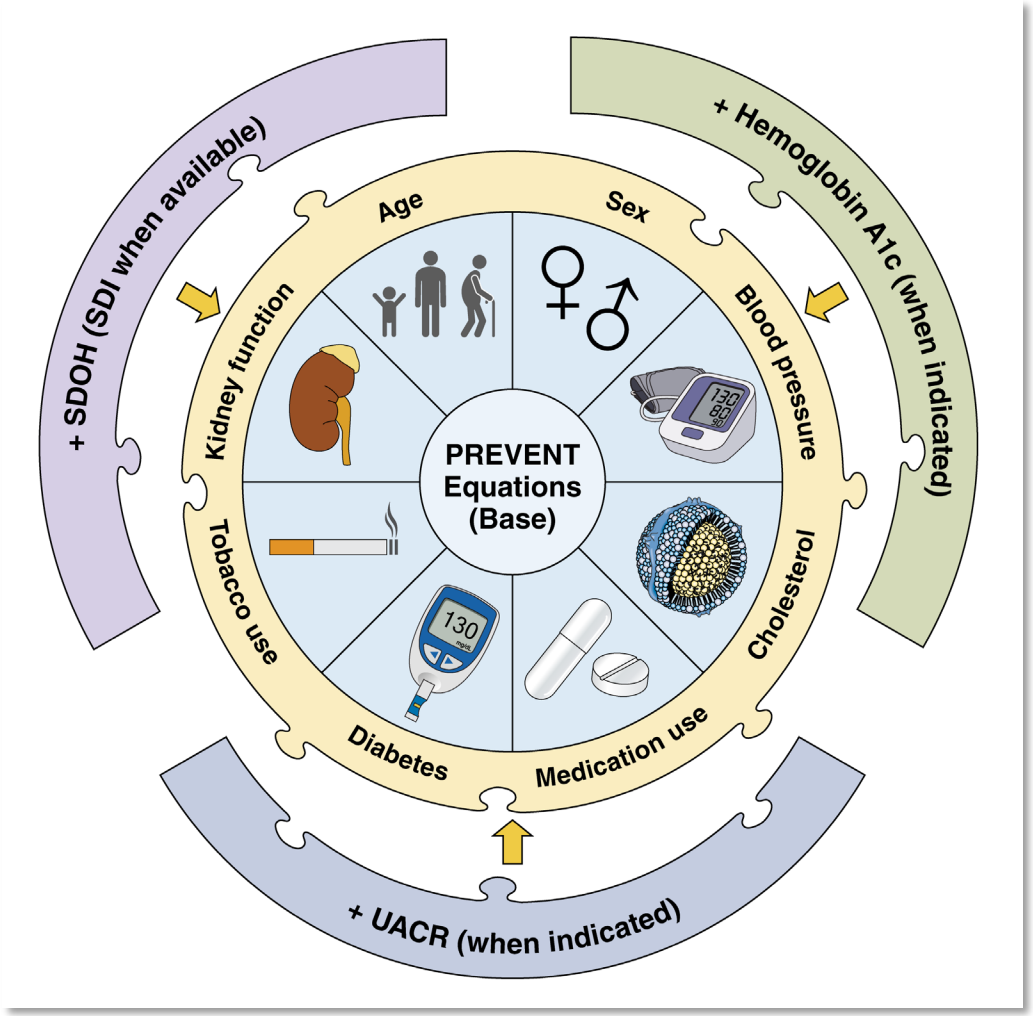


Figure 4. Key Takeaways of the AHA PREVENT Equations
1. Include a large, contemporary, and diverse sample of US adults for derivation and external validation
2. Predict the risk of total or global CVD as a composite of atherosclerotic cardiovascular disease and heart failure as well as for each CVD subtype separately
3. Broaden the outcome to include prediction of heart failure
4. Remove race from risk prediction acknowledging that race is a social construct and not a biological predictor
5. Lower the age to begin risk prediction as early as age 30 years and capture a greater proportion of the adult life course
6. Provide risk estimates for CVD over a 10-year and 30-year time span
7. Offer optional models that incorporate add-on measures of kidney and metabolic health when indicated given the growing burden of cardiovascular-kidney-metabolic (CKM) syndrome
8. Include a measure of place-based social disadvantage (social deprivation index [SDI]) to acknowledge the role of social determinants of health in cardiovascular disease risk

Khan SS et. al. *Circulation* 2023

New paradigm for CVD risk: PREVENT™

PREVENT™ Online Calculator

Welcome to the American Heart Association **Predicting Risk of cardiovascular disease EVENTs** (PREVENT™). This app should be used for primary prevention patients (those without atherosclerotic cardiovascular disease or heart failure) only.

Sex — Male / Female

Age — 30-79 years

Total Cholesterol — 130-320 mg/dL

HDL Cholesterol — 20-100 mg/dL

SBP — 90-200 mmHg

BMI — 18.5-39.9

eGFR — 15-140

Diabetes — No / Yes

Current Smoking — No / Yes

Anti-hypertensive medication — No / Yes

Lipid-lowering medication — No / Yes

The following three predictors are optional for further personalization of risk assessment. When they are clinically indicated or available, please click on yes and enter the value

UACR — No / Yes

HbA1C — No / Yes

Zip Code (for estimating social deprivation index [SDI]) — No / Yes

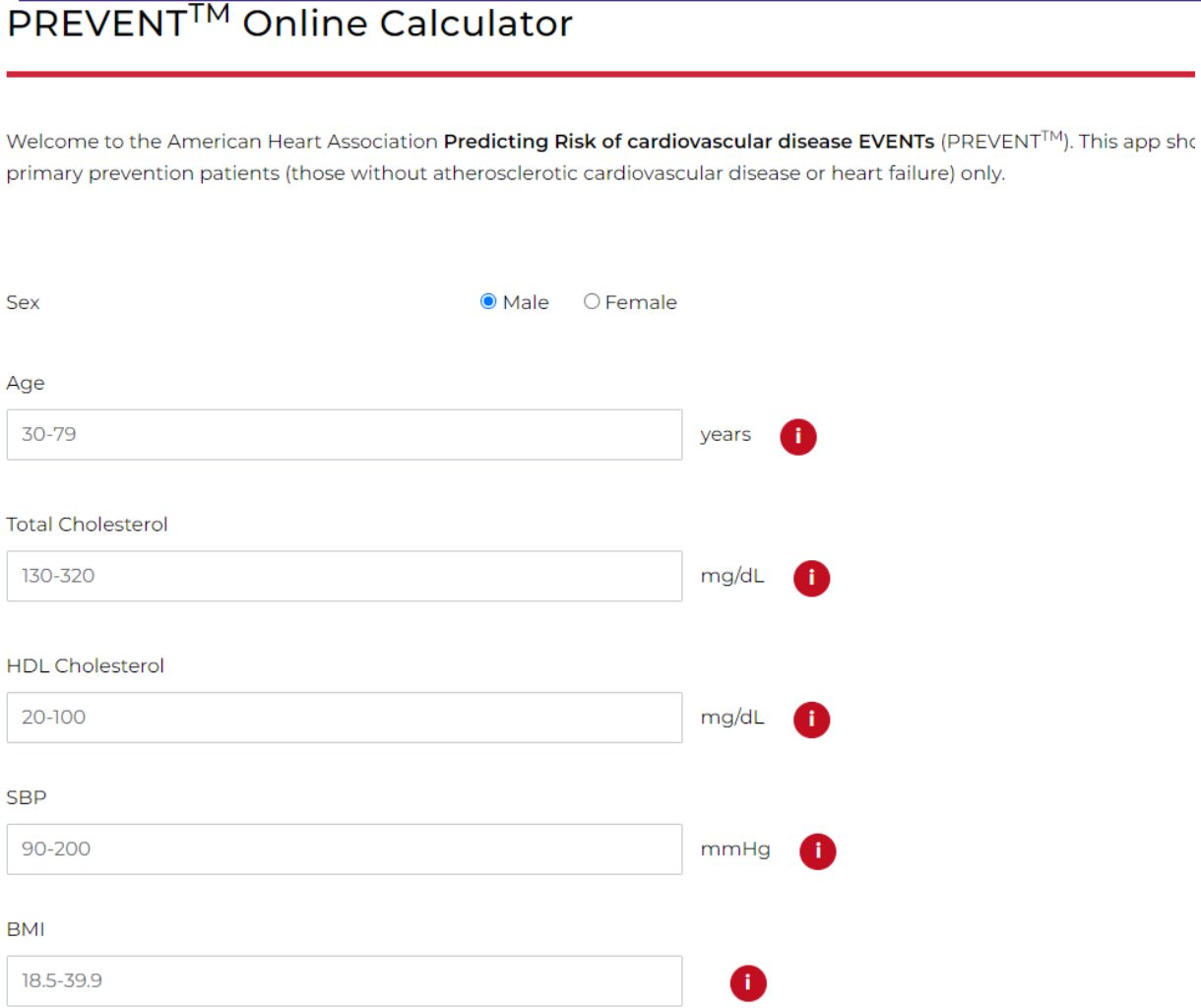
Calculate | Reset

Risk of CVD / Risk of ASCVD / Risk of Heart Failure

https://professional.heart.org/prevent

Khan SS et. al. *Circulation* 2023

New paradigm for CVD risk: PREVENT™



- **Derivation:**
  - 25 datasets
  - N=3,281,919
- **Validation:**
  - 21 datasets
  - N=3,330,085
- **Models:**
  - Sex-specific
  - 10- and 30-year risk estimates
  - Adjusted for competing risk
- **Outcomes:**
  - Total CVD: ASCVD plus HF
  - ASCVD, HF

https://professional.heart.org/prevent

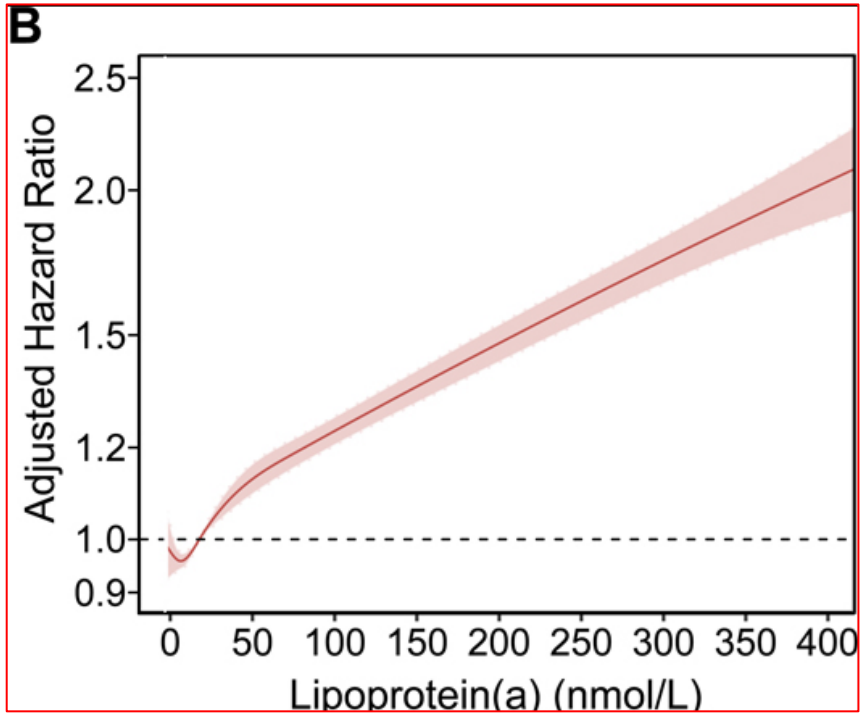
Results: model performance for PREVENT™

	Total CVD		ASCVD		HF	
	Females	**Males**	**Females**	**Males**	**Females**	**Males**
Events	50,324	46,804	31,277	31,328	27,931	23,707
C-Statistic	0.794 (0.763, 0.809)	0.757 (0.727, 0.778)	0.774 (0.743, 0.788)	0.736 (0.710, 0.755)	0.830 (0.816, 0.850)	0.809 (0.777, 0.827)
Calibration Slope (IQI)	1.03 (0.81, 1.16)	0.94 (0.81, 1.13)	1.09 (0.93, 1.33)	1.04 (0.95, 1.19)	1.00 (0.55, 1.15)	0.89 (0.49, 1.07)

Khan SS…Coresh J. Development and Validation of the American Heart Association Predicting Risk of Cardiovascular Disease EVENTs (PREVENT) Equations. *Circulation*. 2023.

Lp(a) as a risk-enhancing factor: How to quantify?

- Log-linear relationship of Lp(a) level with risk



- Approximate updated 10-y risk estimate:

Predicted 10-y risk×[$1.11^{(\text{patient's Lp(a) level in nmol/L}/50)}$]

Example: Patient with 10-yr risk of 10% and

Lp(a) = 250 nmol/L

$10.0\% \times 1.11^{(250/50)} = 10.0\% \times 1.11^{5} = 10.0\% \times 1.69$

$=16.9\%$

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Patel, A.P. *et al.* (2021) 'LP(a) (lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease', *Arteriosclerosis, Thrombosis, and Vascular Biology*, 41(1), pp. 465–474. doi:10.1161/atvbaha.120.315291.

Lifestyle for All!

Particularly important for those with family history/genetic risk

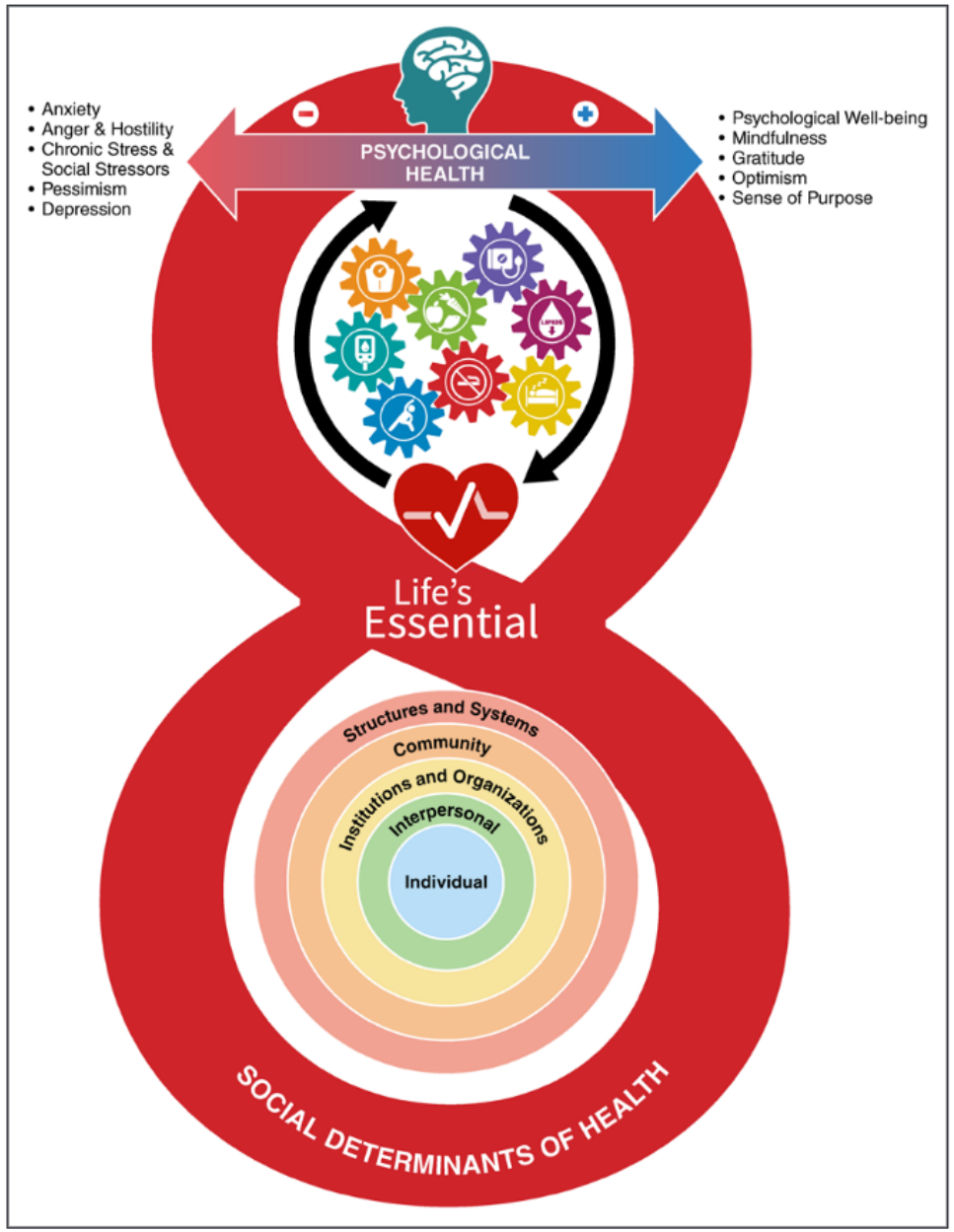
Goals with lifestyle therapy

- Goal is to reduce underlying risk – not to reduce Lp(a) levels directly
- Diet, PA, etc have minimal effects on Lp(a) levels *per se*
- But they can additively reduce risk for CVD events, reducing the background risk through direct effects and indirect effects on other RFs

AHA PRESIDENTIAL ADVISORY

Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association

Donald M. Lloyd-Jones, MD, ScM, FAHA, Chair; Norrina B. Allen, PhD, MPH, FAHA; Cheryl A.M. Anderson, PhD, MPH, MS, FAHA; Terrie Black, DNP, MBA, CRRN, FAHA; LaPrincess C. Brewer, MD, MPH; Randi E. Foraker, PhD, MA, FAHA; Michael A. Grandner, PhD, MTR, FAHA; Helen Lavretsky, MD, MS; Amanda Marma Perak, MD, MS, FAHA; Garima Sharma, MD; Wayne Rosamond, PhD, MS, FAHA; on behalf of the American Heart Association



Lloyd-Jones, D.M. *et al.* (2022) 'Life's essential 8: Updating and enhancing the American Heart Association's construct of Cardiovascular Health: A presidential advisory from the American Heart Association', *Circulation*, 146(5). doi:10.1161/cir.0000000000001078.

What's new?

Updated scoring algorithm for each metric and overall: 0-100 points

Life's Essential 8 contains one new element, SLEEP HEALTH

Defined by sleep duration, or the average hours of sleep a person gets per night

Life's Essential 8

Life's Essential 8 factors

Life's Essential 8 consists of the following vital elements:

4 Health behaviors

- Adequate Sleep
- Healthy Diet
- Not smoking or vaping
- Physical Activity

4 Health factors

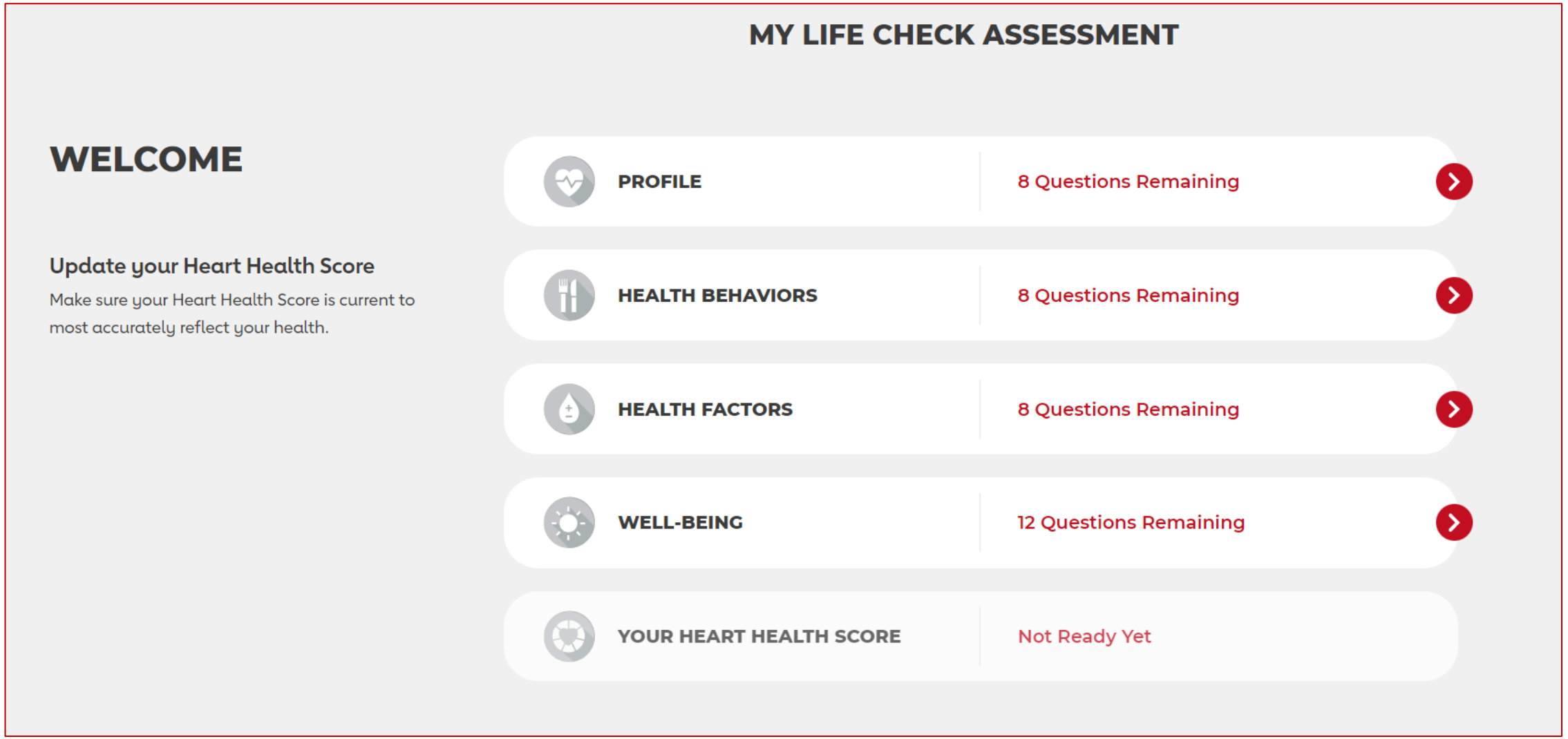
- Blood Pressure
- Blood Sugar
- Blood Lipids
- Healthy Weight

Life's Essential 8

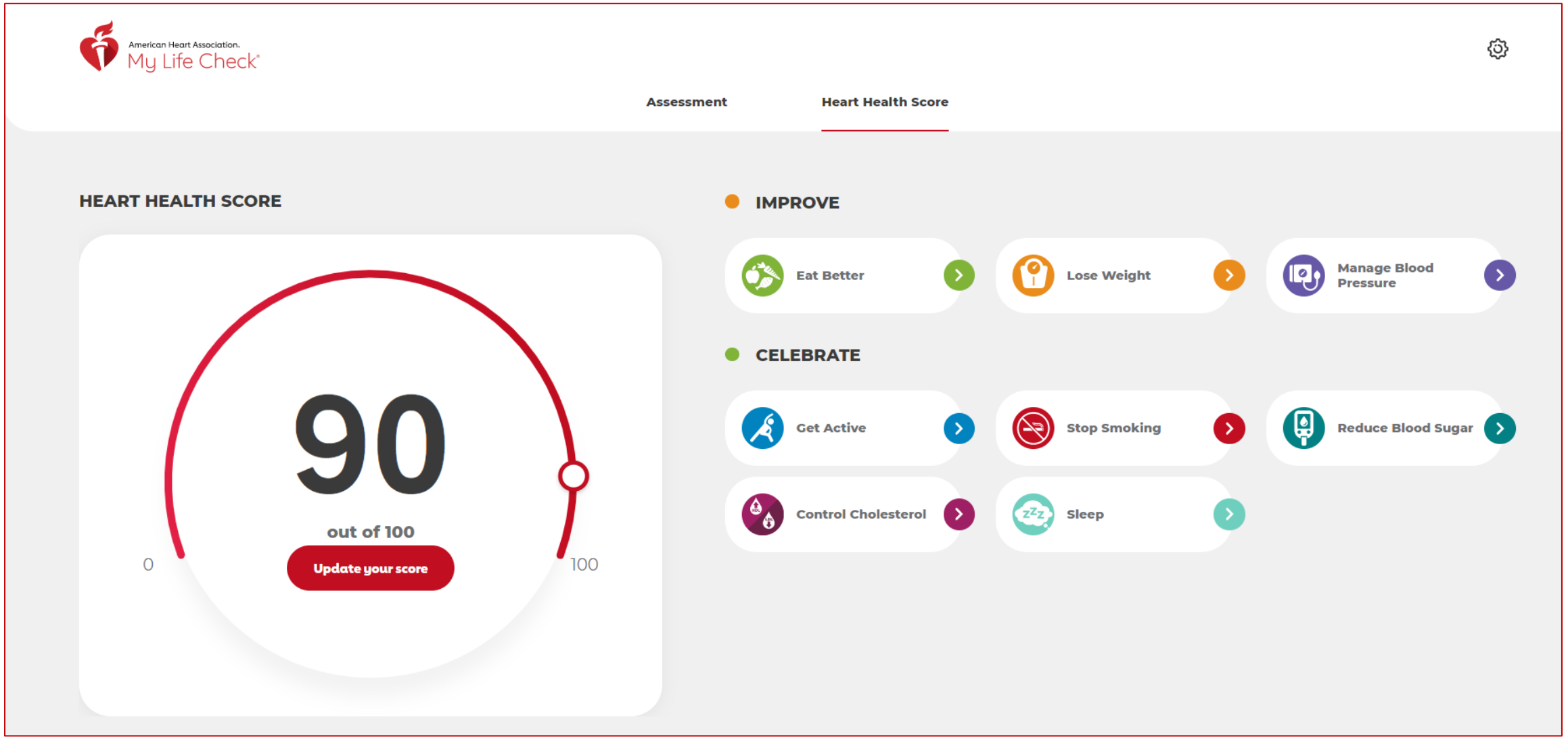
My Life Check

https://mlc.heart.org/

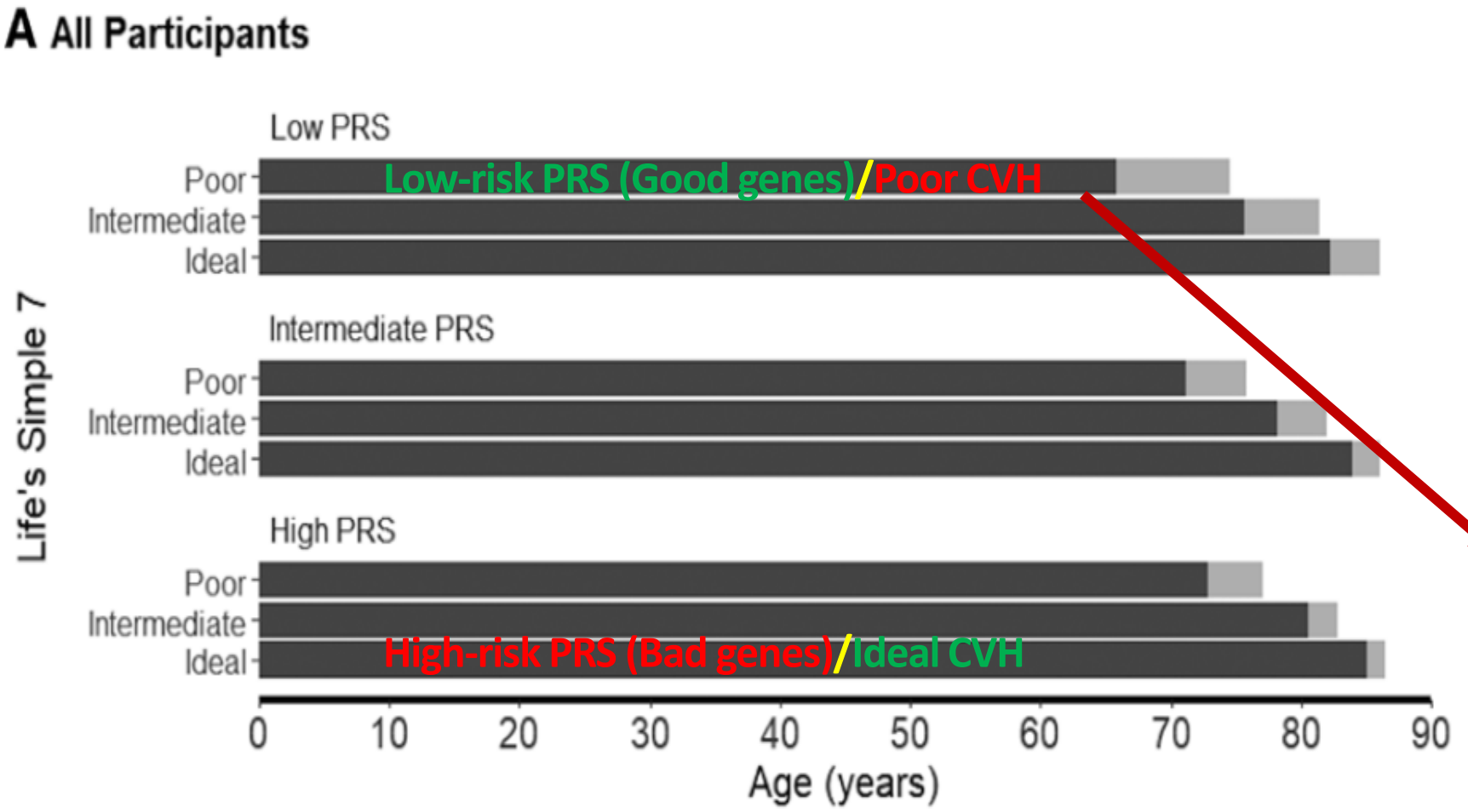
My Life Check - LE8 Assessment and Tracking



My Life Check – Improving LE8



Healthspan and Lifespan by Joint PRS and CVH Status – CVH/Lifestyle Can Mitigate Genetic Risk



12 years longer lifespan

19 years longer healthspan

7 years less with CHD

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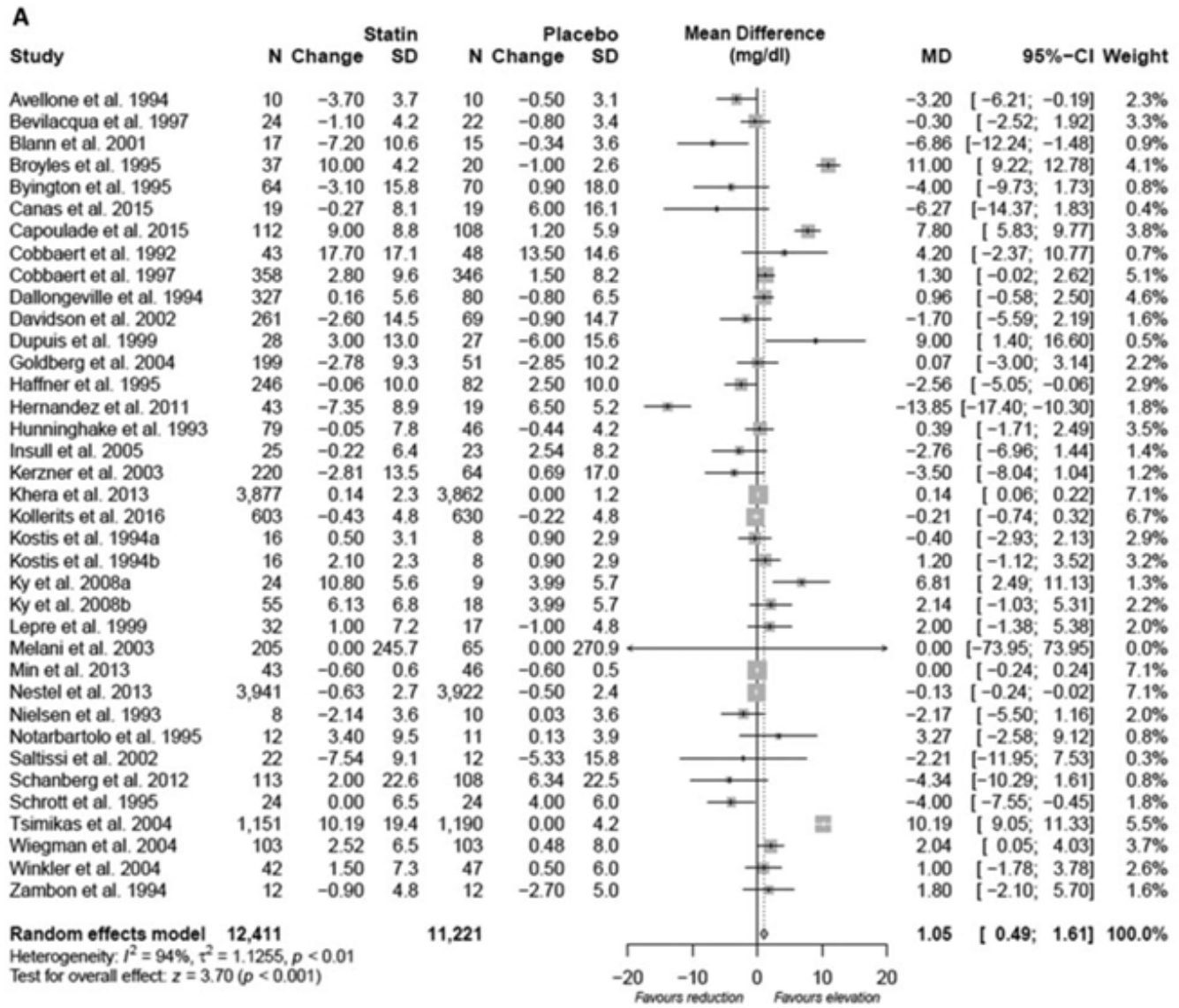
Hasbani, Natalie R et al. "American Heart Association's Life's Simple 7: Lifestyle Recommendations, Polygenic Risk, and Lifetime Risk of Coronary Heart Disease." *Circulation* vol. 145,11 (2022): 808-818. doi:10.1161/CIRCULATIONAHA.121.053730

Medical therapy

LDL-C reduction remains the cornerstone of therapy for now

Statins do not alter Lp(a) levels



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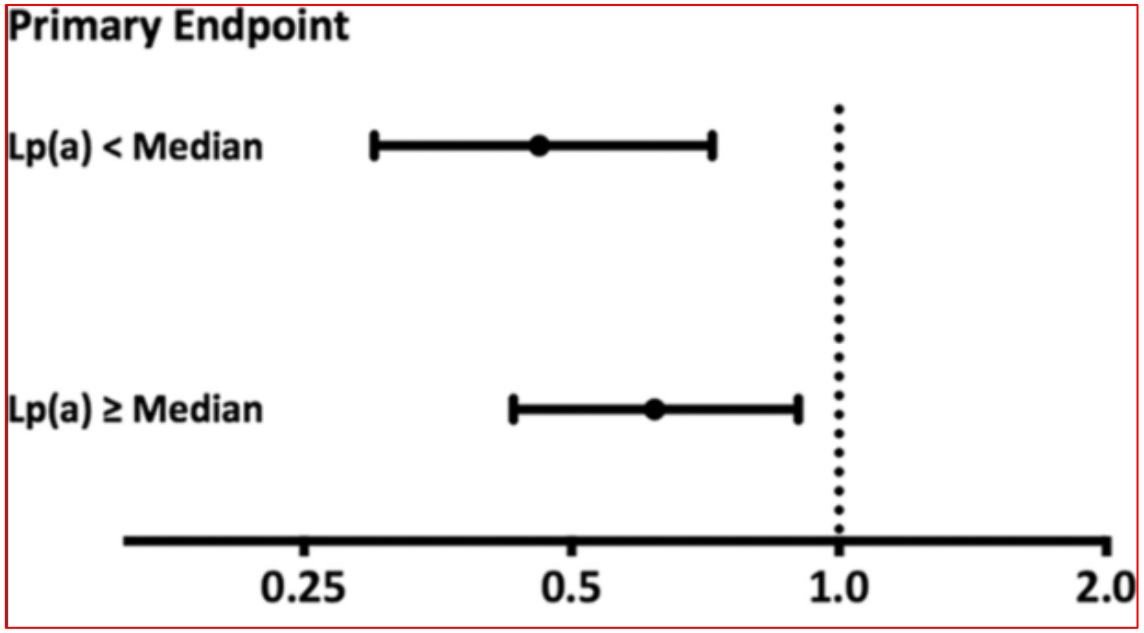
de Boer LM, Oorthuys AOJ, Wiegman A, et al. Statin therapy and lipoprotein(a) levels: a systematic review and meta-analysis. Eur J Prev Cardiol. 2022;29(5):779-792. doi:10.1093/eurjpc/zwab171

Statins reduce ASCVD events – even in people with Lp(a)

- JUPITER trial: Similar RRR, greater ARR with elevated Lp(a)
- BUT Lp(a) represents one mechanisms of “residual risk”



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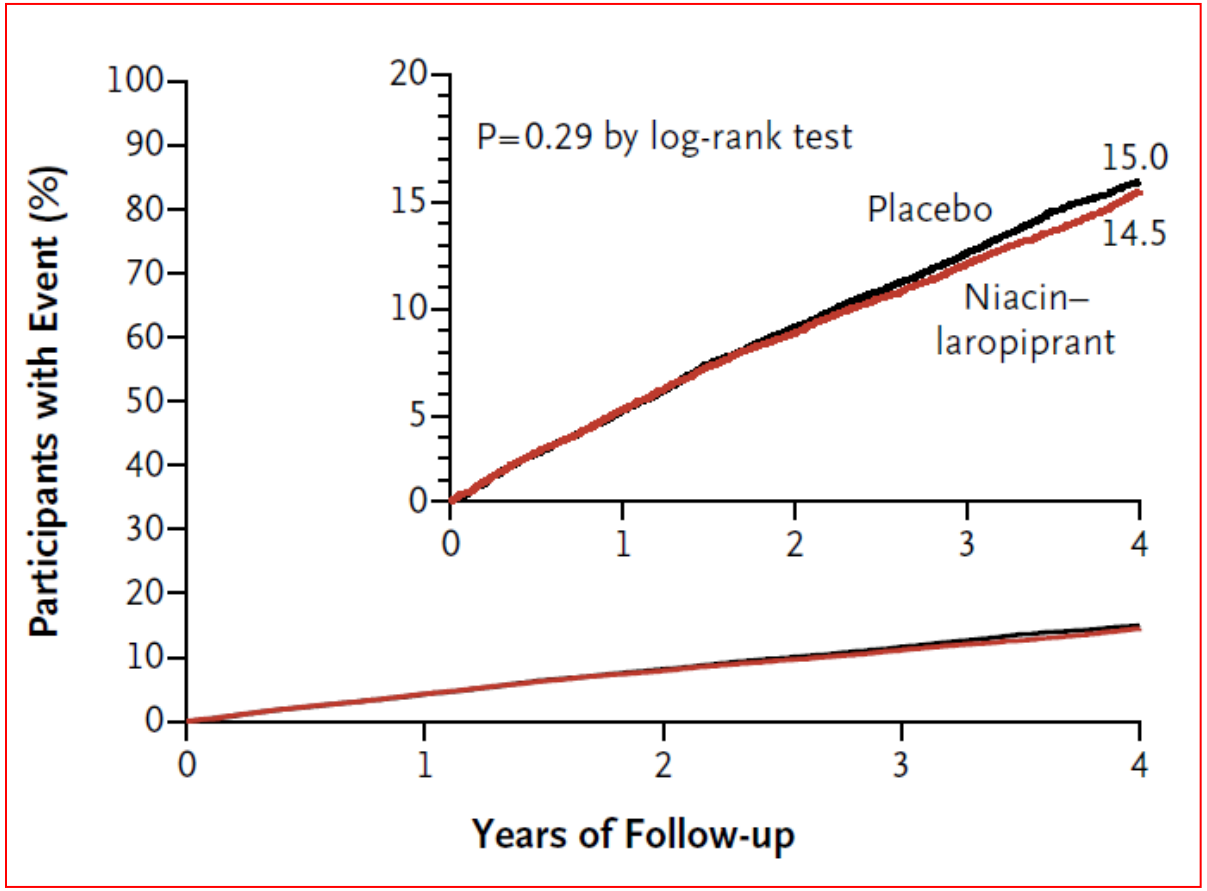
Khera, A.V. *et al.* (2014) ‘Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk’, *Circulation*, 129(6), pp. 635–642. doi:10.1161/circulationaha.113.004406.

Personal approach to care for patients with elevated Lp(a)

- Remove the vector (LDL-C particles)
  - LDL-C <100 mg/dL for primary prevention (ApoB <90)
  - LDL-C <70 mg/dL for high-risk primary and secondary prevention (ApoB <70)
  - LDL-C <55 mg/dL for very high-risk secondary prevention (ApoB <55)
- Checking ApoB can help avoid residual risk related to LDL-C particles
- Consideration of aspirin in higher-risk patients (this appears to be one group with net benefit)

Niacin: HPS2-THRIVE (N=25,000)

ER niacin/laropriprant-simvastatin vs. simvastatin:
<u>No</u> ASCVD event reduction vs placebo-simvastatin



LDL-c	**-10 mg/dL**
HDL-c	**+6 mg/dL**
TG	**-33 mg/dL**

- Usual side effects (skin, GI, HbA1c)
- Increase in GIB, infections
- Borderline increase in mortality

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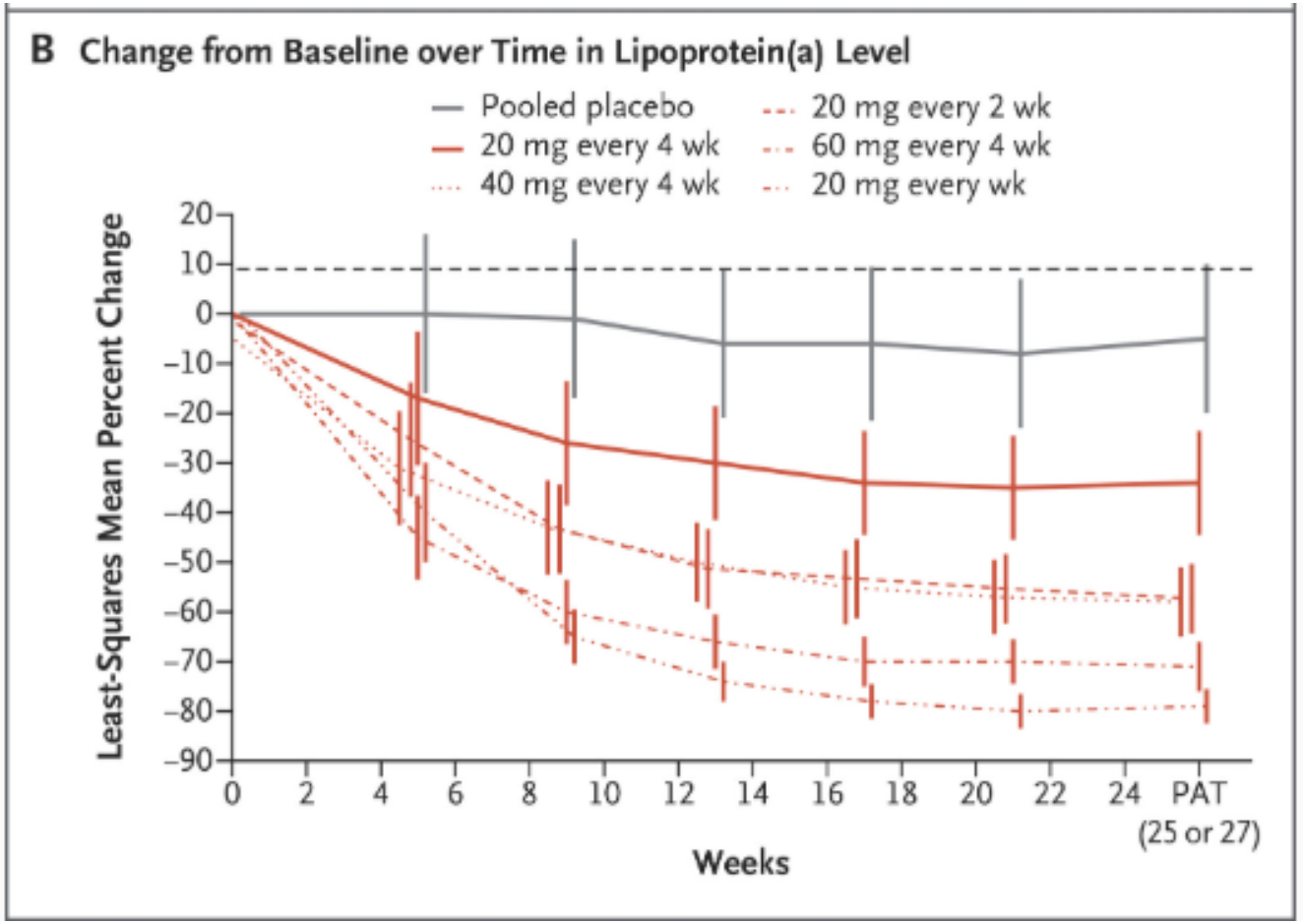
'Effects of extended-release niacin with Laropiprant in high-risk patients' (2014) *New England Journal of Medicine*, 371(3), pp. 203–212. doi:10.1056/nejmoa1300955.

The Future – Direct inhibition of apo(a) production

Pelacarsen – ASO dose-ranging study



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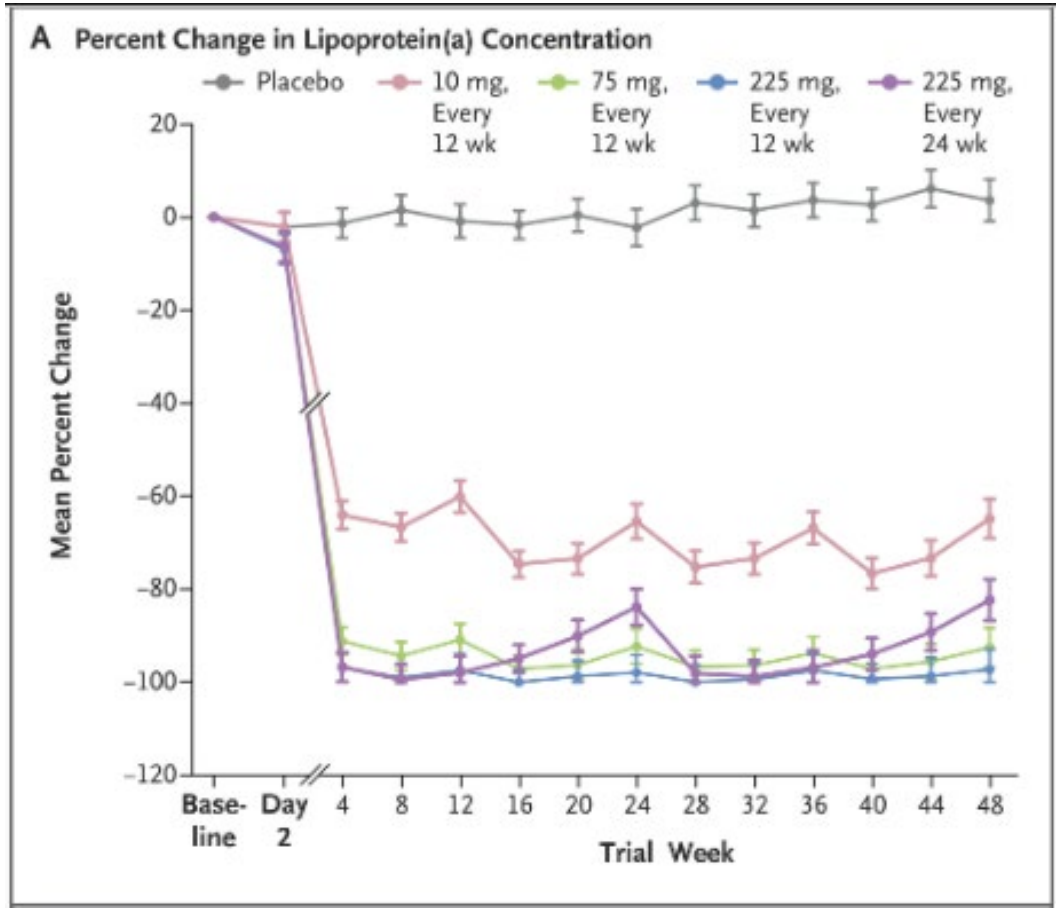
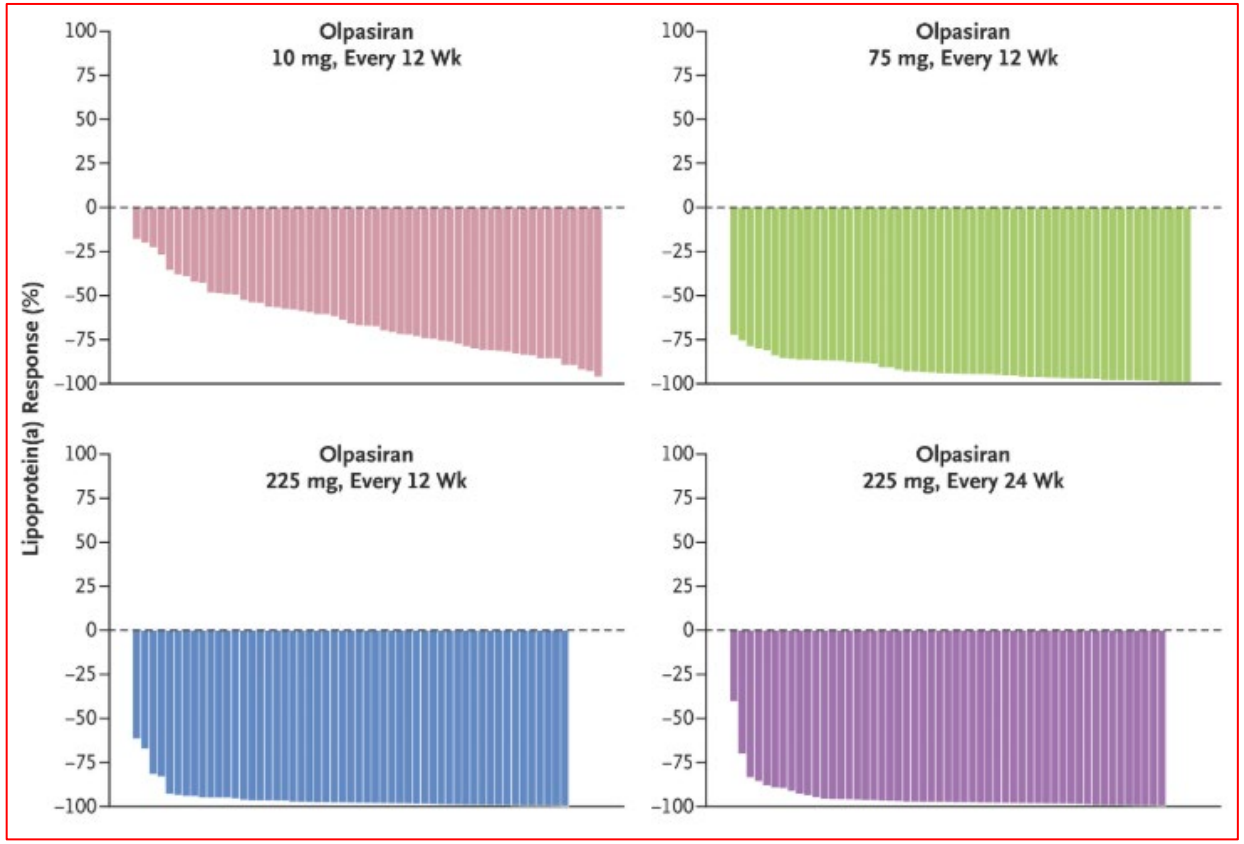
N Engl J Med 2020;382:244-55.
DOI: 10.1056/NEJMoa1905239

Olpasiran – siRNA dose-ranging trial





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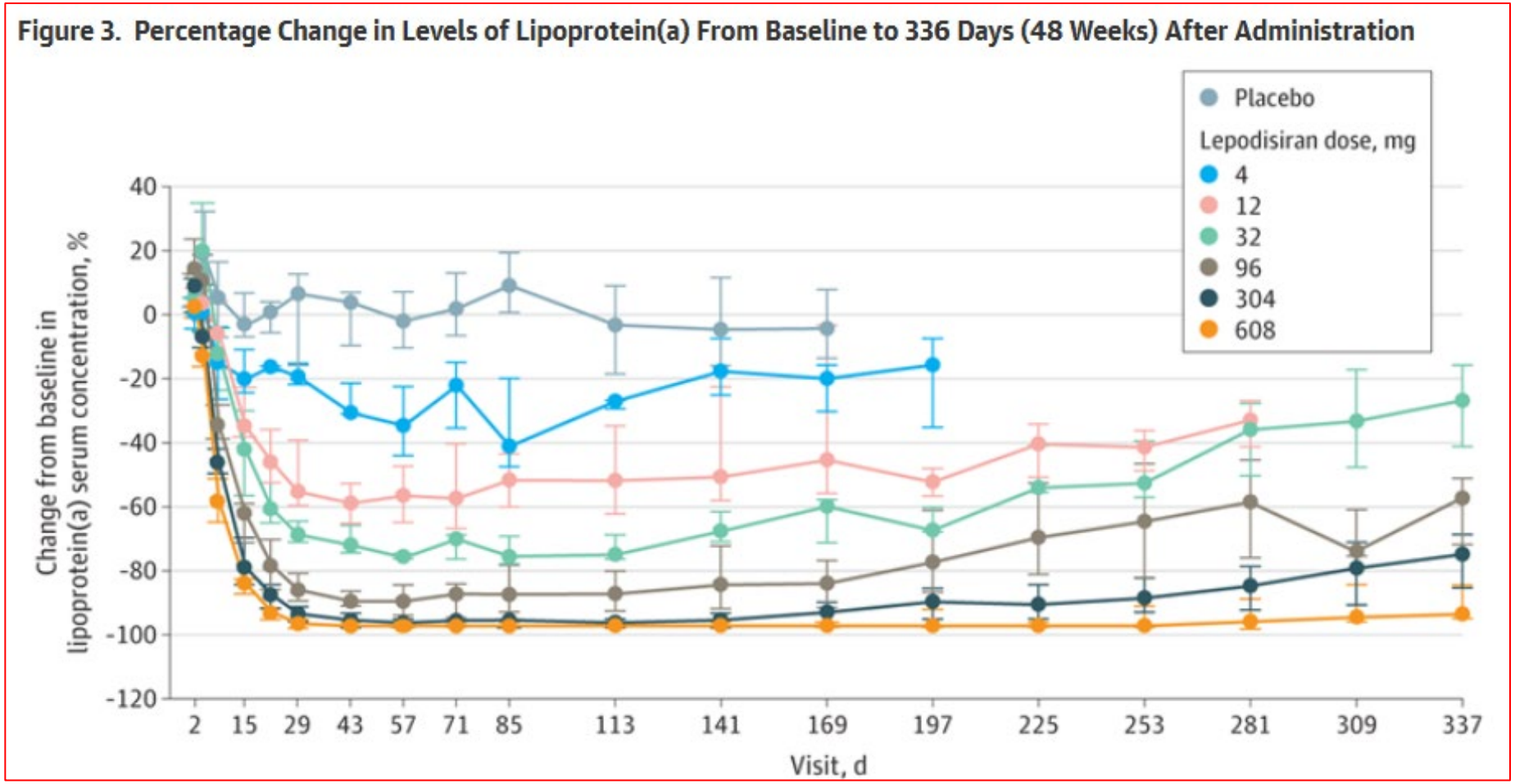
O'Donoghue, M.L. *et al.* (2022) 'Small interfering RNA to reduce lipoprotein(a) in cardiovascular disease', *New England Journal of Medicine*, 387(20), pp. 1855–1864. doi:10.1056/nejmoa2211023.

Lepodisiran – siRNA dose-ranging trial

Figure 3. Percentage Change in Levels of Lipoprotein(a) From Baseline to 336 Days (48 Weeks) After Administration



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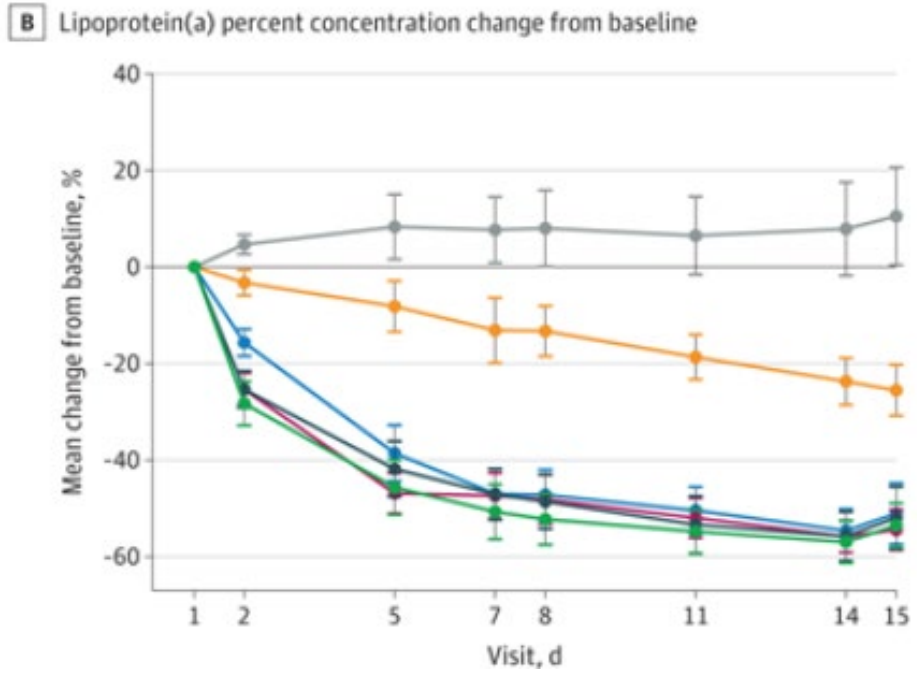
Nissen SE, Linnebjerg H, Shen X, et al. Lepodisiran, an Extended-Duration Short Interfering RNA Targeting Lipoprotein(a): A Randomized Dose-Ascending Clinical Trial. *JAMA.* 2023;330(21):2075–2083. doi:10.1001/jama.2023.21835

Muvalaplin – oral agent

- Blocks covalent binding of apo(a) with apoB-100



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Nicholls SJ, Nissen SE, Fleming C, et al. Muvalaplin, an Oral Small Molecule Inhibitor of Lipoprotein(a) Formation: A Randomized Clinical Trial. *JAMA.* 2023;330(11):1042–1053. doi:10.1001/jama.2023.16503

Take Home Points

- Lp(a) enhances risk for ASCVD, and context of Lp(a) matters
- Managing traditional risk factors with lifestyle and medication remains paramount
- Statins, ezetimibe, and PCSK9mAb can reduce risk with variable effects on Lp(a) itself
- The future of direct Lp(a) therapy looks bright
  - We will answer the “causal question”
  - Direct Lp(a) inhibition may become an important adjunct to LDL-C lowering therapy, if compounds prove safe and efficacious in larger trials (ongoing)

Questions and Discussion

Lp(a) Resources