CMHC
Cardiometabolic Health Congress

www.cardiometabolichealth.org

Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

Lipids in Racial/Ethnic Populations

Keith C. Ferdinand, MD, FACC, FAHA, FASPC, FNLA
Gerald S. Berenson Endowed Chair in Preventative Cardiology
Professor of Medicine
Tulane University School of Medicine
New Orleans, LA

Goals

- Recognize LDL-C reducing mechanisms for established, new and emerging agents
- Discuss safety and efficacy for approved and emerging agents
- Highlight special considerations for research and pharmacotherapy by sex/gender and race/ethnicity

Race/ Ethnicity and Lp(a) Mass Concentrations

Characteristics of Multi-Ethnic study of Atherosclerosis (MESA) Participants in 4 Ethnic Groups at Visit 1

	Black participants	White participants	Chinese American Participants	Hispanic/Latinx Participants
N	1323	1677	548	1044
Age	61 (52-70)	62 (54-71)	62 (53-71)	61 (52-69)
Sex (men)	621 (46.1%)	813 (47.6%)	217 (38.8%)	517 (48.6%)
Non-Lp(a) LDL-C, mg/dL	113 (92-133)	115 (97-136)	114 (96-132)	116 (97-137)
HDL-C, mg/dL	50 (41-61)	50 (41-62)	48 (40-58)*	45 (38-54)*
Triglycerides, mg/dL	89 (66-122)*	110 (75-160)*	121 (85-169)*	133 (94-189)*
Lp(a), mg/dL	35.1 (20.4-61.6)*	12.9 (5.8-29.6)	12.9 (7.7-23.4)	13.1 (6.3-28.8)

Guan, W. et al. Arteriosclerosis, Thrombosis, and Vascular Biology. 2015;35:996-1001

Ferdinand, Bond, Reddy 2021

Which is higher in Black participants of multi-ethnic study of atherosclerosis compared to other ethnic groups?

a) Triglycerides
b) LDL-C
c) Lp(a)
d) All of the above

Guan W, et al. Atherosclerosis, thrombosis, and vascular biology. 2015.

Which is higher in Black participants of multi-ethnic study of atherosclerosis compared to other ethnic groups?

a) Triglycerides
b) LDL-C
c) Lp(a)
d) All of the above

Guan W, et al. Atherosclerosis, thrombosis, and vascular biology. 2015.

ACC/AHA 2018 Cholesterol Guideline

- A new component of management guideline is consideration of race/ethnicity

COR	LOE	Recommendation
IIa	B-NR	For clinical decision-making in adults of different race/ethnicities, reasonable to review race/ethnic features that can influence ASCVD risk so as to adjust choice of statin or intensity of treatment.

Grundy SM, et al. J AM Coll Cardiol. 2018 Nov 8. pii: S0735-1097(18)39034-X

2018 ACC/ AHA Guidelines – Evaluating Racial/ Ethnic Groups

	Asian Americans	Hispanic/Latino Americans	Blacks
Evaluation			
Lipid issues	**Lower levels of HDL-C vs. whites.** **Higher LDL-C** in Asian Indians, Filipinos, Japanese, and Vietnamese vs. whites. **Increased high TG** in all subgroups.	Women - higher prevalence low HDL-C vs. Hispanic/Latino men.	**Blacks higher levels HDL-C, lower levels TG** vs. whites or Hispanic/Latinos
Risk Decisions			
CAC score	South Asian men similar to NH white men, higher than blacks, Latinos, and Chinese Americans. South Asian women similar to whites and other racial/ethnic women; higher in older age	Predicts similarly in whites and Hispanic/Latino.	Highest in white and Hispanic men, **blacks significantly lower prevalence/severity of CAC.**

Adapted from Grundy SM, et al. J AM Coll Cardiol. 2018 Nov 8. pii: S0735-1097(18)39034-X

Ferdinand, Bond, Reddy 2021

2018 ACC/ AHA Guidelines – Evaluating Racial/ Ethnic Groups

	Asian Americans	Hispanic/Latino Americans	Blacks
Evaluation			
Lipid issues	**Lower levels of HDL-C vs. whites.**	Women - higher prevalence low HDL-C vs. Hispanic/Latino men.	**Blacks higher levels HDL-C, lower levels TG** vs. whites or Hispanic/Latinos
	Higher LDL-C in Asian Indians, Filipinos, Japanese, and Vietnamese vs. whites.		
	Increased high TG in all subgroups.		
Risk Decisions			
CAC score	South Asian men similar to NH white men, higher than blacks, Latinos, and Chinese Americans.	Predicts similarly in whites and Hispanic/Latino.	Highest in white and Hispanic men, **blacks significantly lower prevalence/severity of CAC.**
	South Asian women similar to whites and other racial/ethnic women; higher in older age		

Adapted from Grundy SM, et al. J AM Coll Cardiol. 2018 Nov 8. pii: S0735-1097(18)39034-X

Ferdinand, Bond, Reddy 2021

2018 ACC/ AHA Management –Racial/ Ethnic Groups

	Asian Americans	Hispanic/Latino Americans	Blacks
Intensity of statin therapy and response to LDL-C lowering	**Japanese may be sensitive to statin dosing.**	No sensitivity to statin dosage compared with non-Hispanic whites or blacks.	No sensitivity to statin dosage compared with non-Hispanic whites.
Safety	**Higher rosuvastatin levels** in Japanese, Chinese, Malay, and Asian Indians vs whites. **FDA recommends lower starting dose (rosuvastatin 5 mg in Asians** vs 10 mg in whites). Caution as dose uptitrated.	No specific safety issues with statins.	**Baseline serum CK higher** in blacks vs whites. 95th percentile race/ethnicity- and sex-specific serum CK normals available for assessing changes

Adapted from Grundy SM, et al. J AM Coll Cardiol. 2018 Nov 8. pii: S0735-1097(18)39034-X

Ferdinand, Bond, Reddy 2021

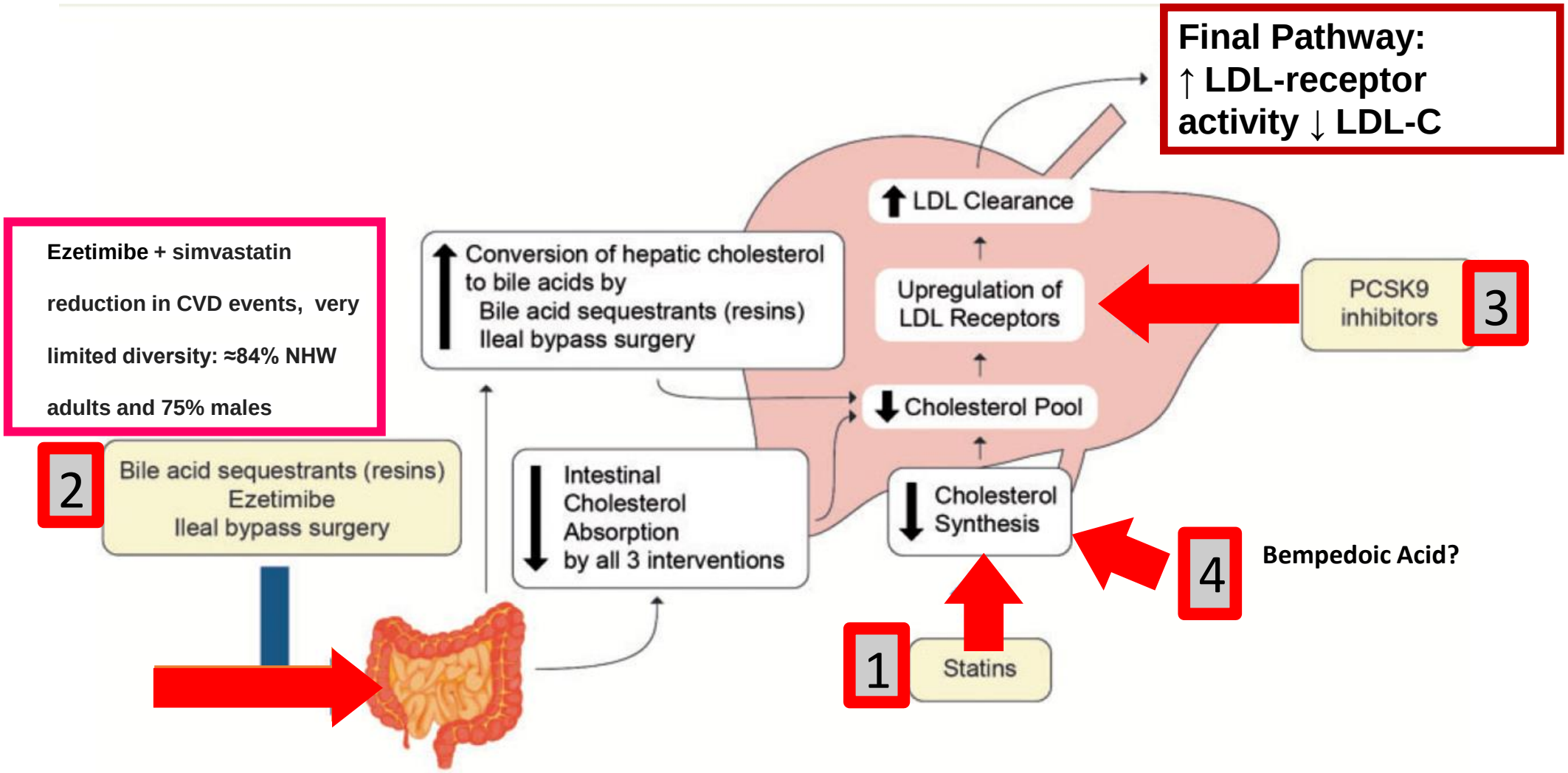
2018 ACC/ AHA Guidelines – Evaluating Racial/ Ethnic Groups

	Asian Americans	Hispanic/Latino Americans	Blacks
Evaluation			
Lipid issues	**Lower levels of HDL-C vs. whites.**	Women - higher prevalence low HDL-C vs. Hispanic/Latino men.	**Blacks higher levels HDL-C, lower levels TG** vs. whites or Hispanic/Latinos
	Higher LDL-C in Asian Indians, Filipinos, Japanese, and Vietnamese vs. whites.		
	Increased high TG in all subgroups.		
Risk Decisions			
CAC score	South Asian men similar to NH white men, higher than blacks, Latinos, and Chinese Americans.	Predicts similarly in whites and Hispanic/Latino.	Highest in white and Hispanic men, **blacks significantly lower prevalence/severity of CAC.**
	South Asian women similar to whites and other racial/ethnic women; higher in older age		

Adapted from Grundy SM, et al. J AM Coll Cardiol. 2018 Nov 8. pii: S0735-1097(18)39034-X

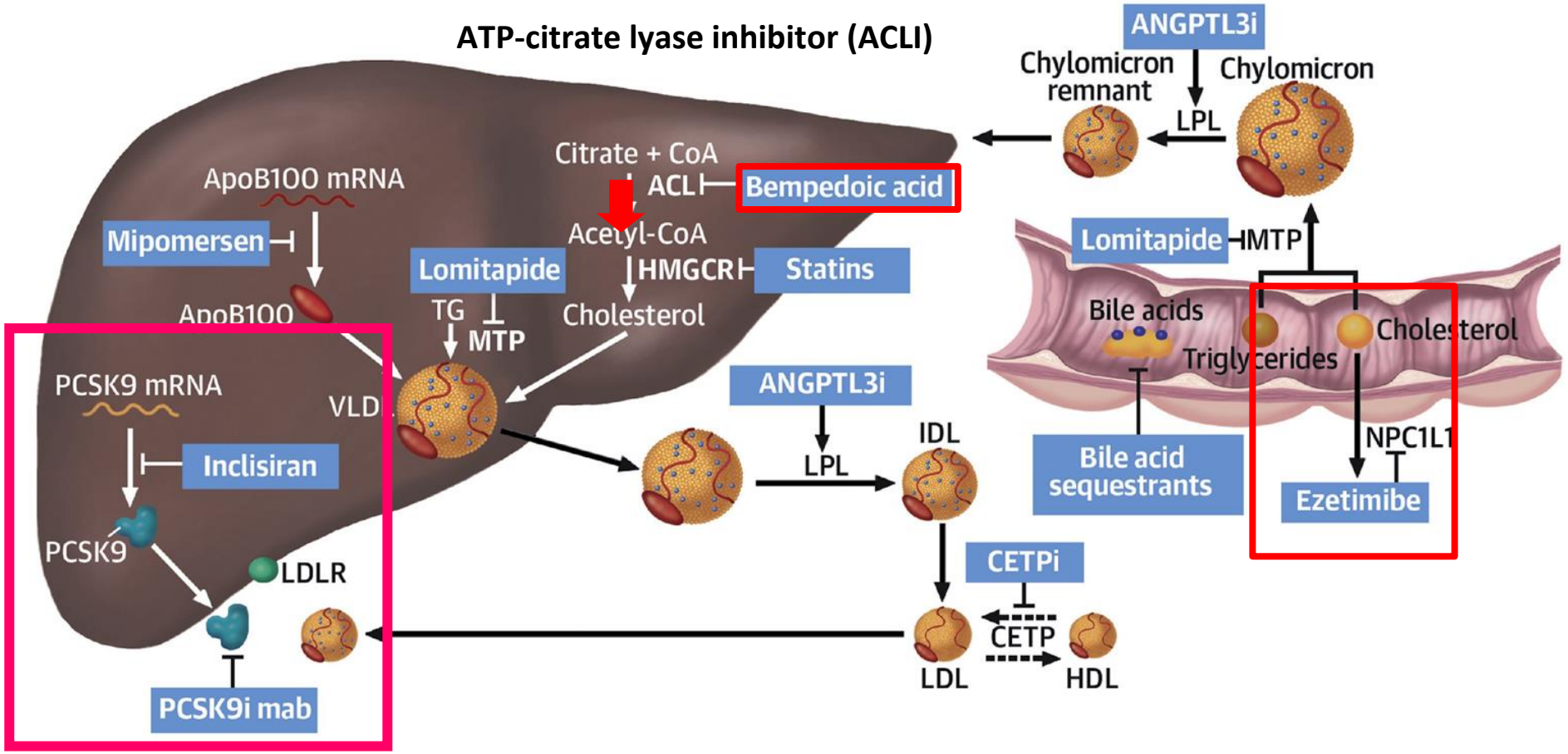
Ferdinand, Bond, Reddy 2021

Mechanisms: 3 Major LDL-Lowering Therapies



Modified from Ference BA, et al. Eur Heart J. 2017;38:2459-2472.

Working Mechanisms of Low-Density Lipoprotein Cholesterol Lowering Therapies



Nurmohamed, N.S. et al. J Am Coll Cardiol. 2021; 77(12):1564-75

Screening for Awareness and Detection of Familial Hypercholesterolemia (CASCADE-FH) registry

Atherosclerosis 267 (2017) 19–26

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

N=3167

S.M. Amrock et al. / Atherosclerosis 267 (2017) 19e26

Our data suggest that Asian and black FH patients are undertreated compared to whites, even if they have already been diagnosed with ASCVD. Racial/ethnic disparities in cardiovascular disease management have been observed previously [43], with nonwhite US minorities less likely to have their cholesterol checked [44], less likely to be on appropriate statin therapy [45,46], and less likely to achieve ideal cardiovascular health [2]. Our analysis of statin use in different races/ethnicities detected global statistically significant differences, but analyses of subgroups were likely underpowered to reach statistical significance. Most concerningly, blacks appeared less likely to have received statins.

Journal of Clinical Lipidology (2019) 13, 586–593

Journal of Clinical Lipidology

Alirocumab efficacy and safety by race and ethnicity: Analysis from 3 ODYSSEY phase 3 trials

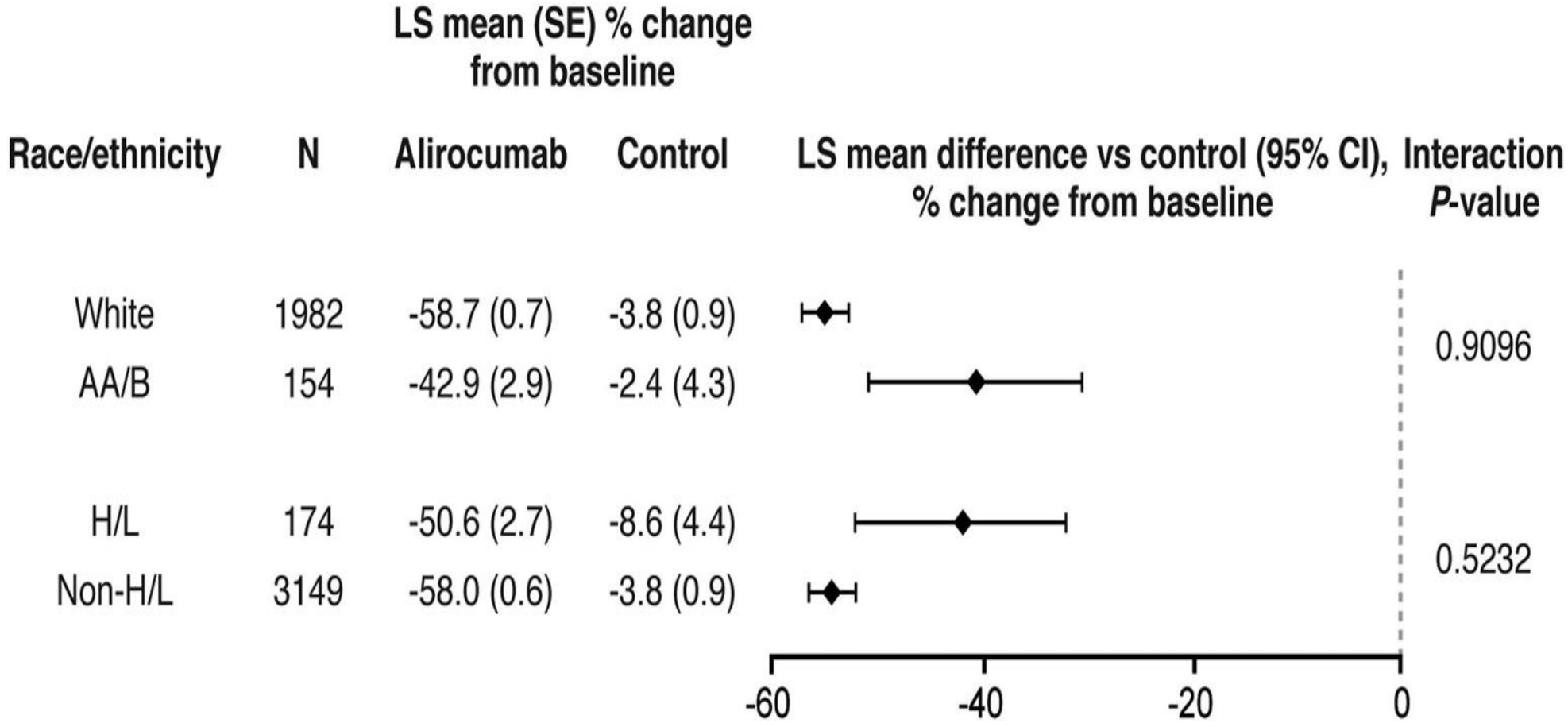
Keith C. Ferdinand, MD*, Terry A. Jacobson, MD, Andrew Koren, MD, Joseph Elassal, MD, Desmond Thompson, PhD, Prakash Deedwania, MD

Baseline characteristics stratified by race and ethnicity (randomized population)

Characteristic	White (N = 3039)	AA/B (N = 156)	P-value comparing white and AA/B	H/L (N = 175)	Non-H/L (N = 3197)	P-value comparing H/L and non-H/L
Male, n (%)	2004 (65.9)	79 (50.6)	.0002	92 (52.6)	2099 (65.7)	.0007

AA/B, African-American/black; Apo, apolipoprotein; H/L, Hispanic/Latino; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein (a); MI, myocardial infarction; Q, quartile; SD, standard deviation.

Percentage change from baseline to week 24 in LDL-C stratified by race and ethnicity (intention-to-treat population).



Journal of Clinical Lipidology 2019 13586-593.e5DOI: (10.1016/j.jacl.2019.06.002)

Circulation: Cardiovascular Quality and Outcomes

ORIGINAL ARTICLE

Effect of Access to Prescribed PCSK9 Inhibitors on Cardiovascular Outcomes

See Editorial by Nasir et al

BACKGROUND: Atherosclerotic cardiovascular disease remains a major cause of death and disability, especially for high-risk familial hypercholesterolemia individuals. PCSK9i (proprotein convertase subtilisin kexin type 9 inhibitors) reduce low-density lipoprotein cholesterol levels and cardiovascular event rates. However, PCSK9i prescriptions are rejected at high rates by payers, and use is often delayed or eventually abandoned as a treatment option. We tested the hypothesis that acute coronary syndromes, coronary interventions, stroke, and cardiac arrest are more prevalent in patients with rejected or abandoned PCSK9i prescriptions than for those with paid PCSK9i prescriptions.

Kelly D. Myers, BS*
Niloofar Farboodi, MSc, MPH*
Mkaya Mwamburi, MD, PhD, MA
William Howard, PhD
David Staszak, PhD
Samuel Gidding, MD
Seth J. Baum, MD
Katherine Wilemon, BS
Daniel J. Rader, MD

Circ Cardiovasc Qual Outcomes. 2019;12:e005404.

Circulation: Cardiovascular Quality and Outcomes

ORIGINAL ARTICLE

Effect of Access to Prescribed PCSK9 Inhibitors on Cardiovascular Outcomes

CONCLUSIONS: Individuals in the rejected and abandoned cohorts had significantly increased risk of cardiovascular events compared with those in the paid cohort. Rejection, abandonment, and disparities related to PCSK9i prescriptions are related to higher cardiovascular outcome rates.

as a treatment option. We tested the hypothesis that acute coronary syndromes, coronary interventions, stroke, and cardiac arrest are more prevalent in patients with rejected or abandoned PCSK9i prescriptions than for those with paid PCSK9i prescriptions.

Seth J. Baum, MD
Katherine Wilemon, BS
Daniel J. Rader, MD

Circ Cardiovasc Qual Outcomes. 2019;12:e005404.

The Impact on CV Outcomes of High Rates of Prescription Denials and Abandonment

- **Women, minorities, and those with lower education or lower income levels** were **less likely** to receive approval for a PCSK9i prescription and were less likely to fill an approved prescription.

Circ Cardiovasc Qual Outcomes. 2019;12:e005404.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 29, 2018 VOL. 379 NO. 22

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, J.M. Edelberg, S.G. Goodman, C. Hanotin, R.A. Harrington, J.W. Jukema, G. Lecorps, K.W. Mahaffey, A. Moryusef, R. Pordy, K. Quintero, M.T. Roe, W.J. Sasiela, J.-F. Tamby, P. Tricoci, H.D. White, and A.M. Zeiher, for the ODYSSEY OUTCOMES Committees and Investigators*

Characteristic	Alirocumab (N = 9462)	Placebo (N = 9462)
Age — yr	58.5±9.3	58.6±9.4
Female sex — no. (%)	2390 (25.3)	2372 (25.1)
Race — no. (%)†		
White	7500 (79.3)	7524 (79.5)
Asian	1251 (13.2)	1247 (13.2)
Black	235 (2.5)	238 (2.5)
Other	475 (5.0)	451 (4.8)

Schwartz, Gregory G., et al. *New England Journal of Medicine* 379.22 (2018): 2097-2107.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 4, 2017 VOL. 376 NO. 18

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

Characteristic	Alirocumab (N=9462)	Placebo (N=9462)
Age — yr	58.5±9.3	58.6±9.4
Female sex — no. (%)	2390 (25.3)	2372 (25.1)
Race — no. (%)†		
White	7500 (79.3)	7524 (79.5)
Asian	1251 (13.2)	1247 (13.2)
Black	235 (2.5)	238 (2.5)
Other	475 (5.0)	451 (4.8)

Sabatine, Marc S., et al. *New England Journal of Medicine* 376.18 (2017): 1713-1722.

New and Emerging Pharmacotherapies for Lipid Lowering

ABNORMALITIES

- Despite being in a higher risk group, increased PCSK9i rejection observed, notably in women, racial minority, and lower-income groups
- The efficacy and safety of alirocumab by race and ethnicity (NHB, NHW and Hispanic/Latinx participants) has been demonstrated. At baseline, LDL-C levels were similar across treatment groups.
- Similarly, evolocumab significantly reduced LDL-C among four different racial/ethnic groups: results were consistent across Black, Asian, Hispanic/Latinx and non-White (AI/AN, Hawaiian, mixed raced) participants

The NEW ENGLAND JOURNAL of MEDICINE

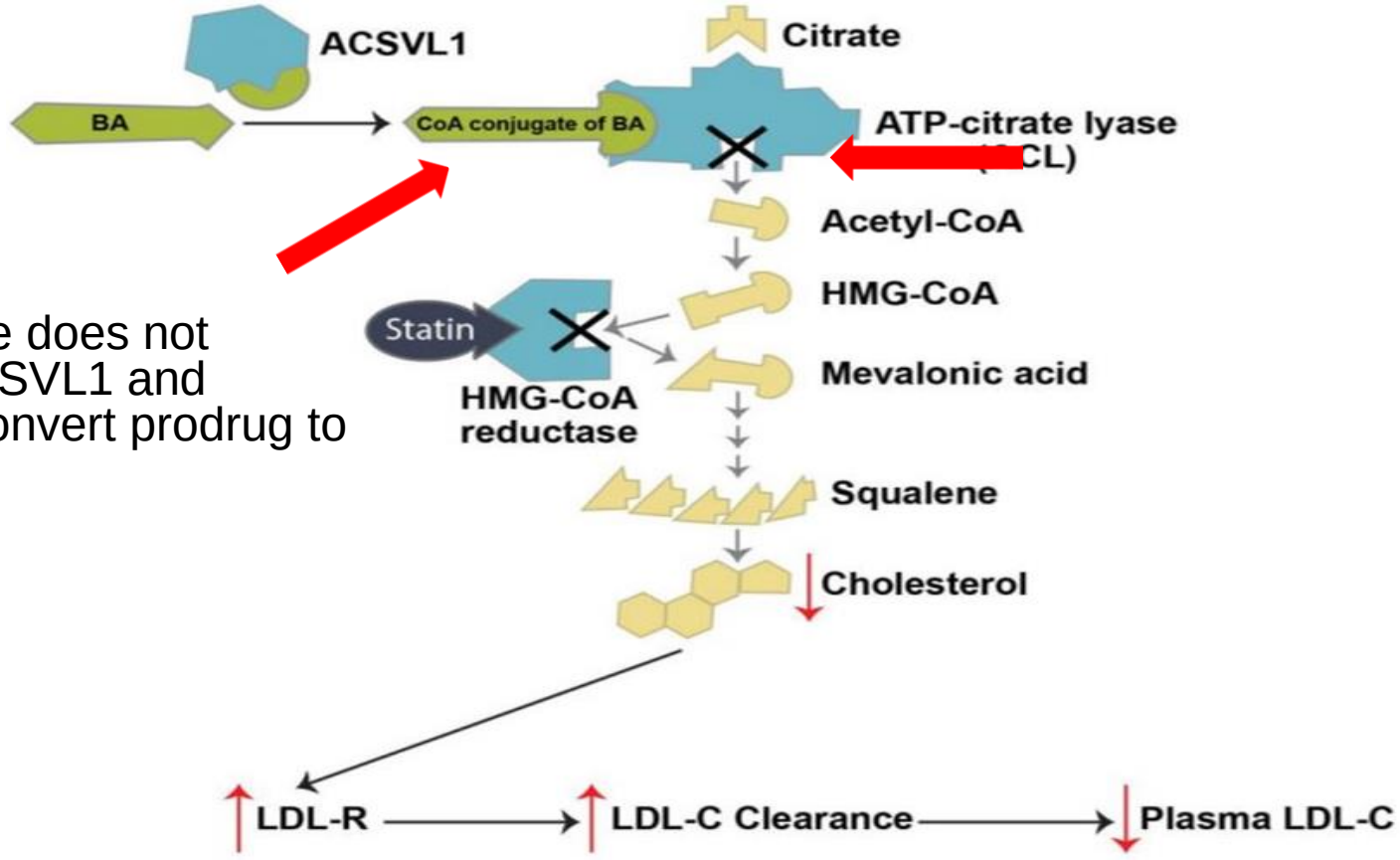
ORIGINAL ARTICLE

Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol

Kausik K. Ray, M.D., M.Phil., Harold E. Bays, M.D., Alberico L. Catapano, Ph.D., Narendra D. Lalwani, Ph.D., M.B.A., LeAnne T. Bloedon, M.S., R.D., Lulu R. Sterling, Ph.D., Paula L. Robinson, M.S., and Christie M. Ballantyne, M.D., for the CLEAR Harmony Trial*

Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C

Skeletal muscle does not express ACSVL1 and unable to convert prodrug to active form



Ray KK et al. N Engl J Med 2019;380:1022-1032.

New Agent Targeting Triglyceride: Icosapent Ethyl

- Significantly reduced major adverse ASVCD events in a landmark trial (N=8,179).
- Widely endorsed for risk reduction with ASCVD (and/or with other risk factors) and hypertriglyceridemia on maximally tolerated statins,
- However, demographics >90% as White subjects.

New And Emerging Pharmacotherapies For Lipid Lowering

ABNORMALITIES

- Bempedoic acid approved by FDA for heterozygous familial hypercholesterolemia (HeFH) or ASCVD
- Cohorts over 95% NHW adults, 3% NHB adults, 1% Asian adults, or 3% Hispanic/Latinx adults and 1% other races
- Inclisiran, roughly 85% ORION-10 and 95% in ORION-11 NHW subjects.

Bempedoic Acid – Clear Outcomes Trial

Table 1. Demographic and Baseline Patient Characteristics in the Intention-to-Treat Population.*

Characteristic	Bempedoic Acid (N = 6992)	Placebo (N = 6978)
Age		
Mean — yr	65.5±9.0	65.5±8.9
Distribution — no. (%)		
<65 yr	2859 (40.9)	2907 (41.7)
≥65 to <75 yr	3070 (43.9)	3027 (43.4)
≥75 yr	1063 (15.2)	1044 (15.0)
Female sex — no. (%)	3361 (48.1)	3379 (48.4)
White race — no. (%)†	6397 (91.5)	6335 (90.8)
Hispanic or Latinx — no. (%)†	1190 (17.0)	1143 (16.4)

Nissen SE et al. N Engl J Med 2023;388.15:1353 - 1364.

Emerging Therapies for Familial Hypercholesterolemia

- Familial hypercholesterolemia, one of the most common genetic disorders, with approximately 1 out of 250 individuals with HeFH, is documented across multiple racial/ethnic populations.
- Women were less likely than men to achieve LDL-C goals and to receive statins; and Asian American and Black participants were 40–50% less likely to achieve LDL-C goals than White counterparts .

Inclisiran: Small Interfering Double-Stranded RNA

- Harnesses the natural process of RNA interference
- Nucleotides modified for durability and low immunogenicity
- Distributed to liver due to GalNAc conjugation
- Inhibits production of PCSK9 in hepatocytes

Fitzgerald et al. N Engl J Med. 2017;376:41-51

TABLE 2 Demographic and Clinical Characteristics of Study Participants at Baseline (ITT)

	Inclisiran (n = 1,833)	Placebo (n = 1,827)
Age, yrs	64.1 ± 9.98	63.9 ± 9.87
Male	1,226 (66.9)	1,244 (68.1)
White race*	1,670 (91.1)	1,708 (93.5)
Concomitant lipid modifying therapy		
Statins	1,686 (92.0)	1,675 (91.7)
High-intensity statin	1,356 (74.0)	1,345 (73.6)
Ezetimibe	251 (13.7)	270 (14.8)

TABLE 2 Demographic and Clinical Characteristics of Study Participants at Baseline (ITT)

	Inclisiran (n = 1,833)	Placebo (n = 1,827)
Age, yrs	64.1 ± 9.98	63.9 ± 9.87
Male	1,226 (66.9)	1,244 (68.1)
White race*	1,670 (91.1)	1,708 (93.5)
Concomitant lipid modifying therapy		
Statins	1,686 (92.0)	1,675 (91.7)
High-intensity statin	1,356 (74.0)	1,345 (73.6)
Ezetimibe	251 (13.7)	270 (14.8)

Wright RS et al. JACC. 2021; 77.9: 1182-1193

CMHC Cardiometabolic Health Congress

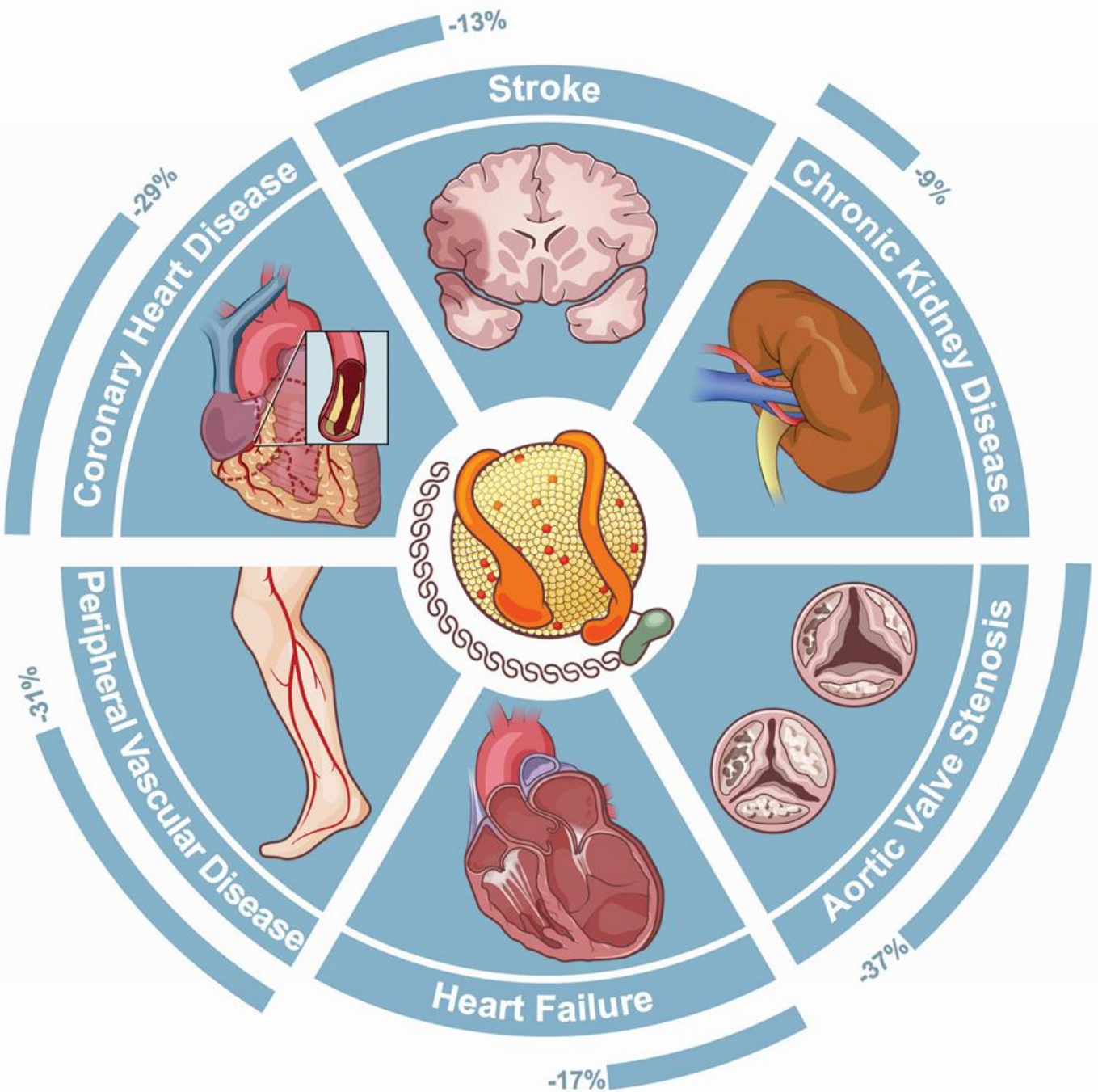
www.cardiometabolichealth.org

Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

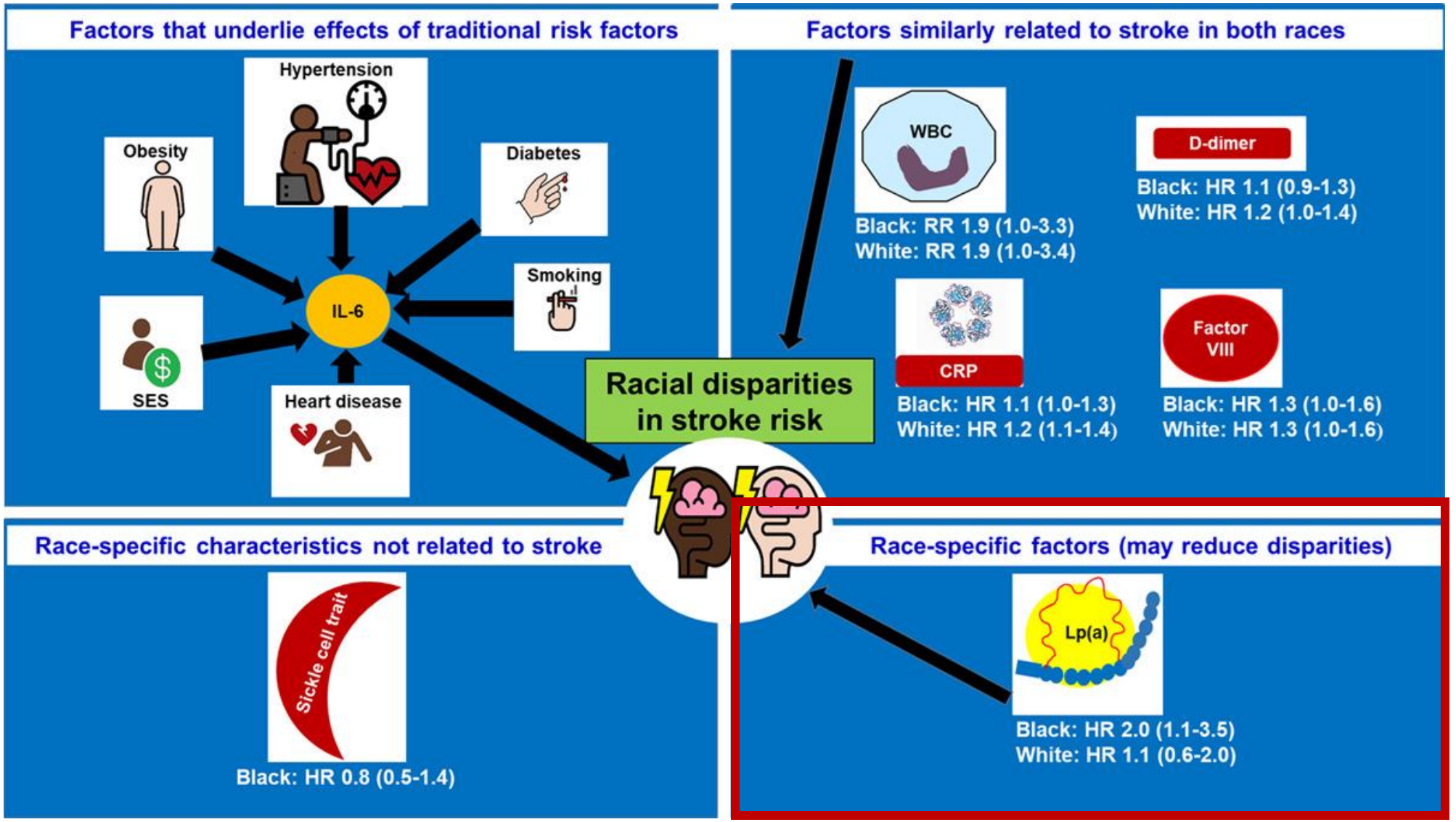
Lipoprotein(a) / Lp(a)

Keith C. Ferdinand, MD, FACC, FAHA, FASPC, FNLA
Gerald S. Berenson Endowed Chair in Preventative Cardiology
Professor of Medicine
Tulane University School of Medicine
New Orleans, LA



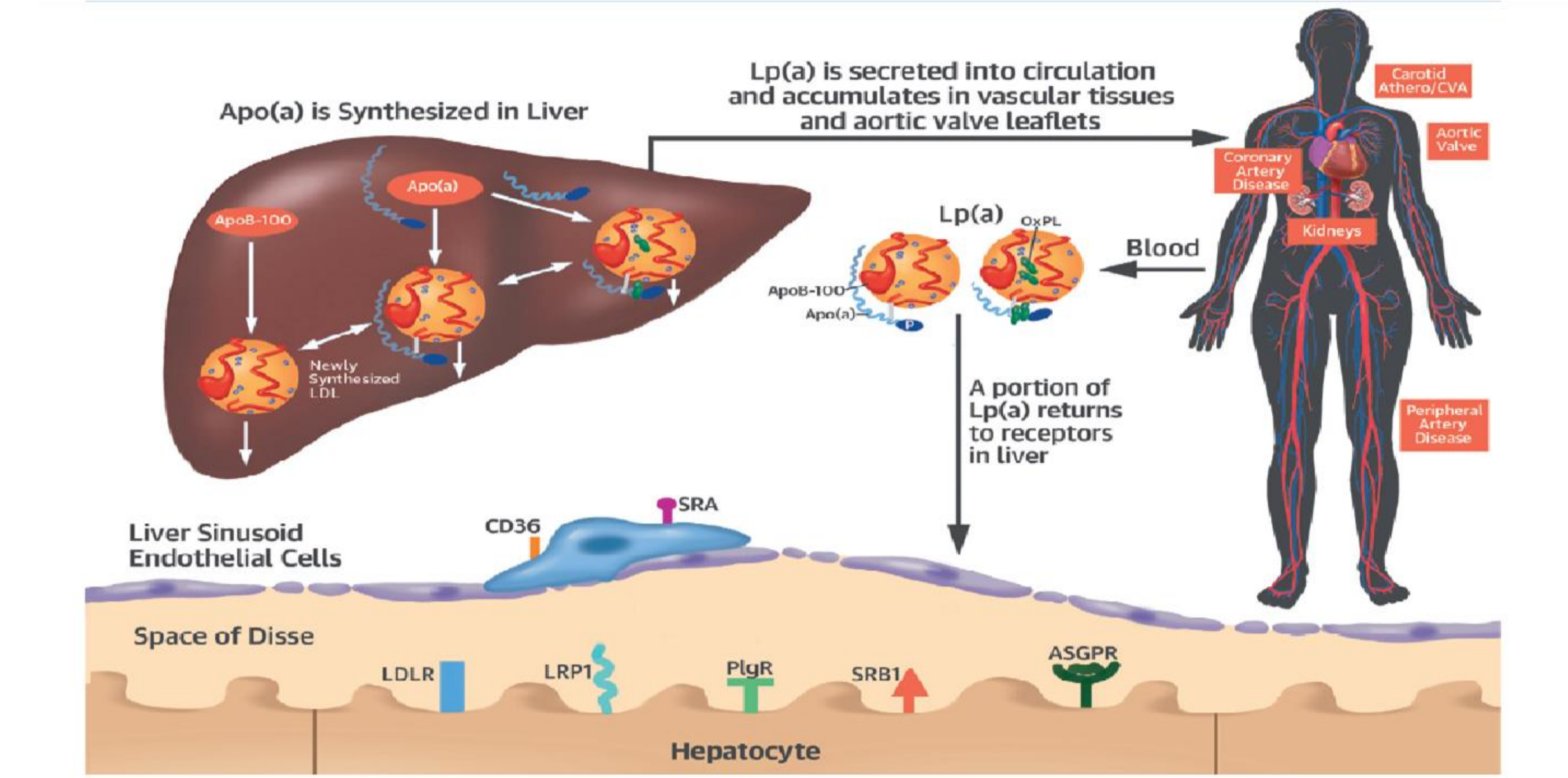
Emdin et al JACC 2016;68:2761-72

Identifying Genetic and Biological Determinants of Race-Ethnic Disparities in Stroke in the US



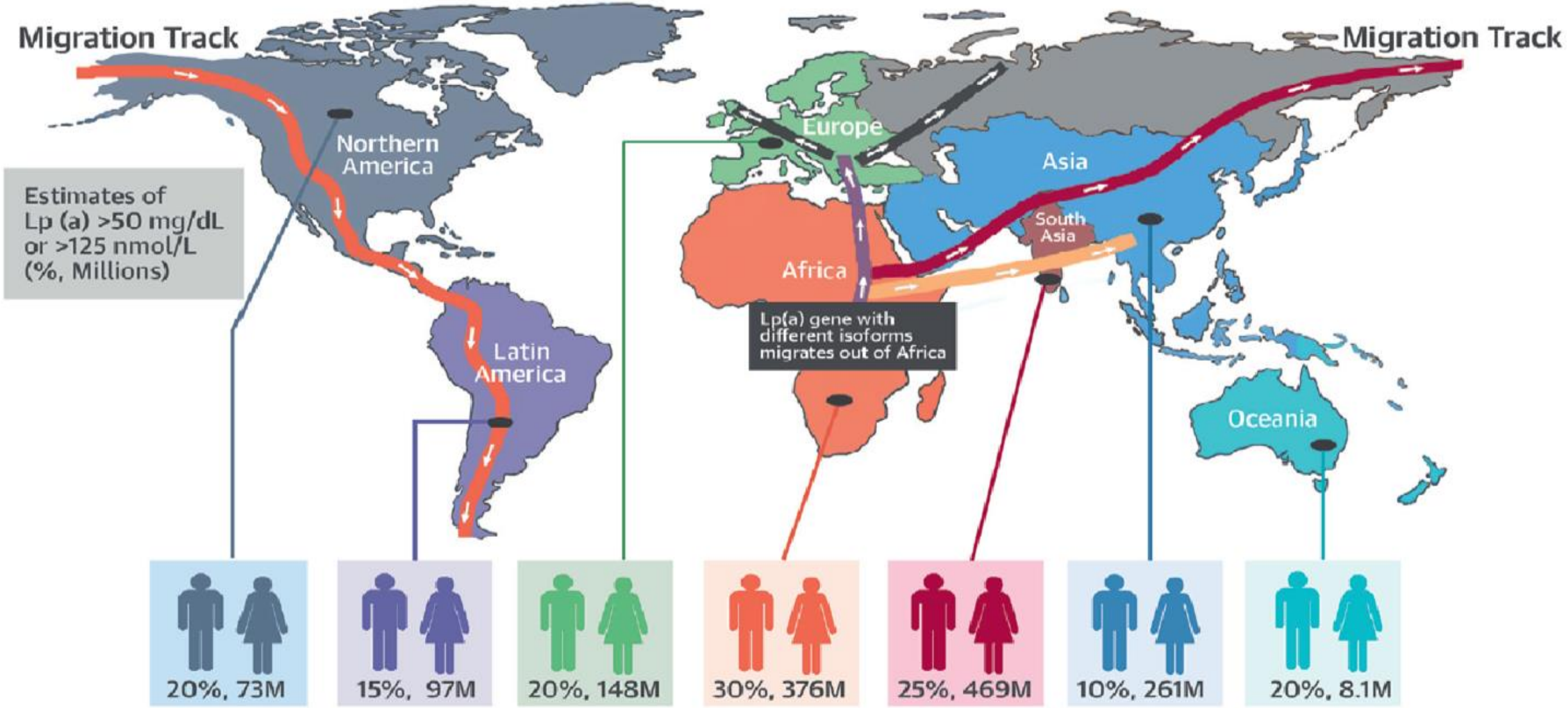
Mukaz, DK et al Stroke. 2020;51:3417–3424

Lp(a) Metabolism



Tsimikas, S. et al. J Am Coll Cardiol. 2018;71(2):177–92

Estimated World Population with Elevated Lp(a) > 50mg/dl= 1.43 Billion



Tsimikas, S. et al. JACC. 2018;71(2):177–92

Which estimated world population has the highest percentage of elevated Lp(a)?

a) North America
b) Latin America
c) South Asia
d) Oceania

Tsimikas, S. et al. JACC. 2018;71(2):177–92

Which estimated world population has the highest percentage of elevated Lp(a)?

a) North America
b) Latin America
c) South Asia
d) Oceania

Tsimikas, S. et al. JACC. 2018;71(2):177–92

Emerging Therapies Targeting Lipoprotein(a):

- APO(a)-LRx sustained reduction in Lp(a) levels, data mainly in NHW subjects (> 95%).

Emerging Therapies for Familial Hypercholesterolemia

- Evinacumab, a monoclonal antibody against angiopoietin-like 3 (ANGPTL3), significantly reduces TG and LDL-C by 49% with no serious adverse events reported (68).
- Although approved by the FDA for HoFH in 2021, early data are in mainly in White cohorts.

Lipoprotein abnormalities in South Asians and ASCVD

- South Asian immigrants Lp(a) levels that are similar to those in their counterparts in their home country.
- Lp(a) levels Indian immigrants in West London vs. siblings in Punjab: Lp(a) similar in both populations,
- But were significantly higher (P = 0.01) than those of a white European population in London.

Lp(a):Unique Aspects in AAs

- Nearly 2-fold higher in AAs than in whites
- Jackson Heart Study: informative markers African ancestry at LPA locus strongly associated with Lp(a) level
- ARIC: AA's Lp(a) positively associated with CVD events

Jacobson,T. Et al Journal of Clinical Lipidology Volume 9, Issue 6, Pages S1-S122.e1

Jackson Heart Study (JHS) Genetics and Lp(a)

OPEN ACCESS Freely available online

PLoS one

Single-Nucleotide Polymorphisms in *LPA* Explain Most of the Ancestry-Specific Variation in Lp(a) Levels in African Americans

Rahul C. Deo[1,2,3]*, James G. Wilson[4,5], Chao Xing[6], Kim Lawson[7], W. H. Linda Kao[8], David Reich[1,9], Arti Tandon[1], Ermeg Akylbekova[5,10], Nick Patterson[1,9], Thomas H. Mosley Jr.[5], Eric Boerwinkle[7], Herman A. Taylor Jr.[5,10,11]

Deo, R.C., et al PLoS One 2011 Jan 24;6(1):e14581

Jackson Heart Study (JHS) Genetics and Lp(a)

- Lp(a) levels vary widely between populations
- African-derived populations nearly 2X higher Lp(a) levels than European Americans.
- JHS : genetic basis of this difference in 4464 AAs panel of up to 1447 ancestry informative markers, to accurately estimate African ancestry proportion of each individual at each position in the genome.

Deo, R.C., et al PLoS One 2011 Jan 24;6(1):e14581

Demographic Characteristics for the Genotyped Jackson Heart Study Participants

	All	Unrelated	Unrelated with only African local ancestry at *LPA*	Unrelated with European local ancestry at *LPA*
Number	4464	3300	1[illegible]31	[illegible]5
Male (%)	36.8	37.8	3[illegible]4	[illegible].7
Age (mean - years, ± std.)	55±13	56±11	5[illegible]±12	[illegible]±12
BMI (mean - kg/m^2 ± std.)	32±7	32±7	3[illegible]±7	[illegible]±6
Type II DM (%)	18.9	20.4	2[illegible]6	[illegible].6
Cholesterol or TG-Lowering Medication (%)	12.5	13.6	1[illegible]8	[illegible].3
LDL-Cholesterol: unmedicated | medicated participants (mg/dL)	127±36 | 113±33	128±37 | 113±33	1[illegible]±36 | 113±35	[illegible]0±38 | 117±30
HDL-Cholesterol: unmedicated | medicated participants (mg/dL)	51±14 | 51±14	52±15 | 52±14	5[illegible]±15 | 51±14	[illegible]±14 | 52±12
Serum Triglycerides: unmedicated | medicated participants (mg/dL)	106±81 | 129±151	107±83 | 130±164	1[illegible]±97 | 136±212	[illegible]8±63 | 123±73
Serum Lp(a): unmedicated | medicated participants (mg/dL)	57±44 | 72±54	57±43 | 73±54	62±43 | 83±57	42±37 | 55±43
Overall African Ancestry (%)	83±9	82±9	85±7	75±12

Characteristics are shown for the 4464 genotyped participants, the 3300 unrelated individuals, the 1831 unrelated individuals with homozygous African local ancestry at the *LPA* locus, and the 615 individuals with at least one ancestral European allele at *LPA*.

doi:10.1371/journal.pone.0014581.t001