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Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

Lipoprotein(a): Science, evidence, management and emerging therapies

Sotirios Tsimikas, MD
Director of Vascular Medicine
Professor of Medicine
University of California San Diego

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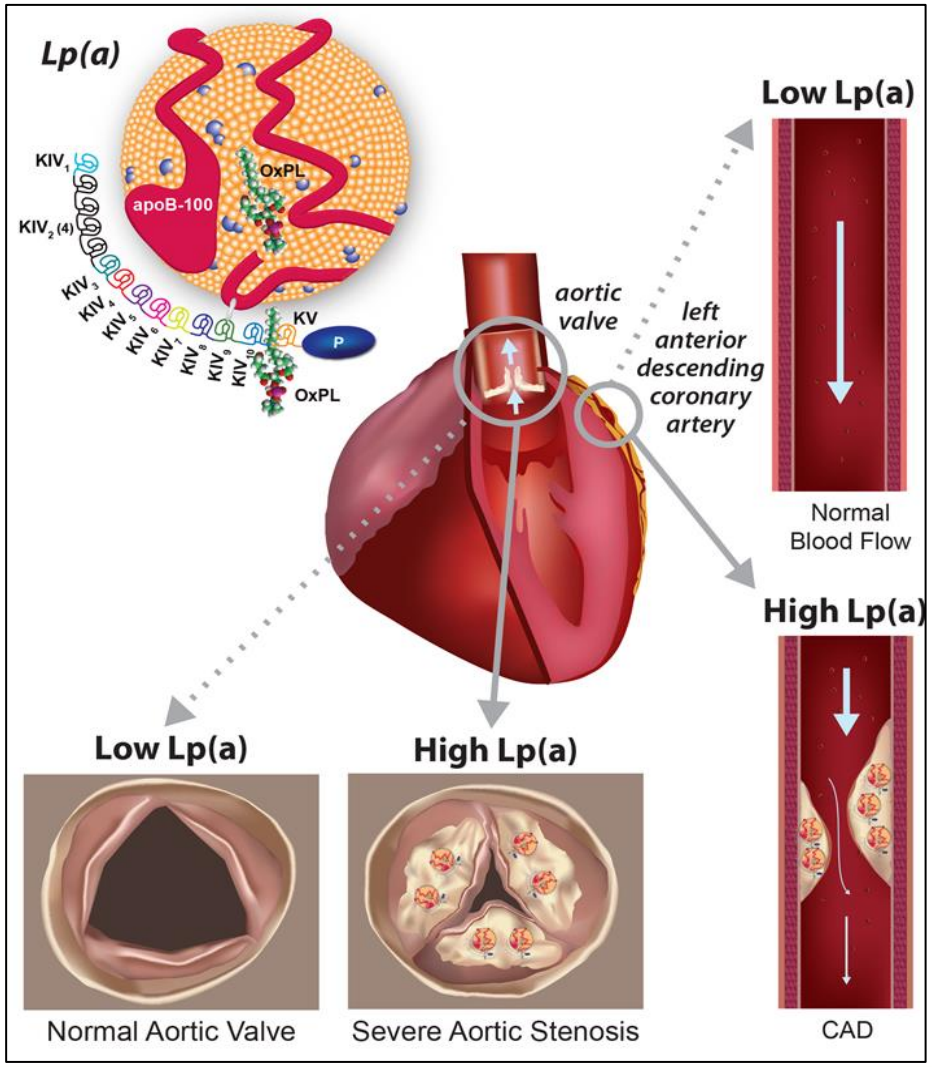
Lipoprotein(a): Prevalence, Pathophysiology, and Role in ASCVD Risk

Sotirios Tsimikas, MD
Director of Vascular Medicine
Professor of Medicine
University of California San Diego

Lipoprotein(a)

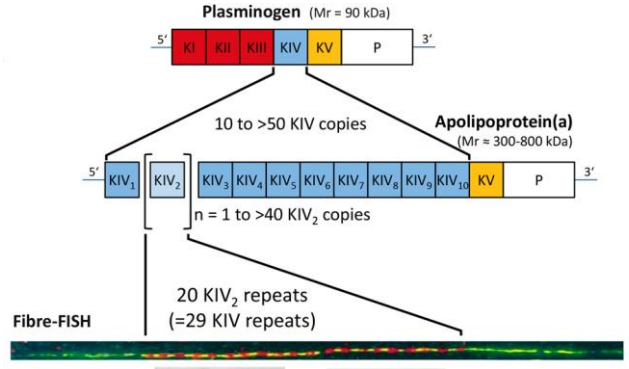
A highly prevalent untreated risk factor for cardiovascular disease & aortic stenosis



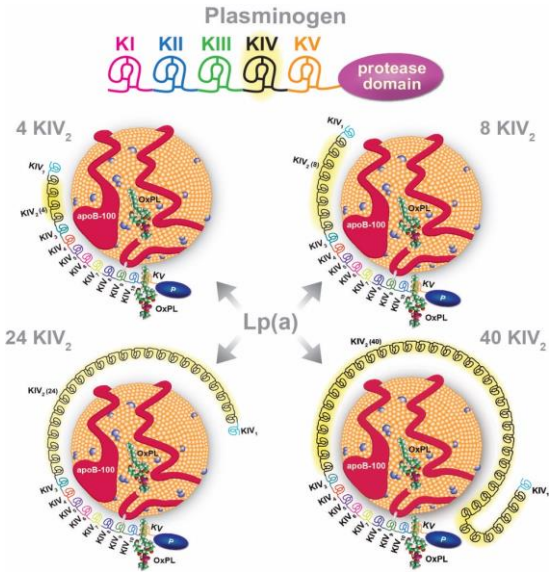
- **Lp(a) levels are genetically determined at birth**
- **Elevated Lp(a) levels cause cardiovascular disease through multiple mechanisms**
  - **Atherogenicity through LDL moiety**
  - **Anti-fibrinolytic activity**
  - **Pro-inflammatory effects of oxidized phospholipids**
- **Elevated levels are recognized as a major untreated cardiovascular risk factor**
- **No approved pharmacological therapies**

Genetics of LPA gene, Relationship to Plasminogen, Oxidized Phospholipids and Clinical Phenotypes

Kare Berg, 1963. A New serum type system in man--the Lp system. Acta Path Microbiol Scand 59: 369-382.

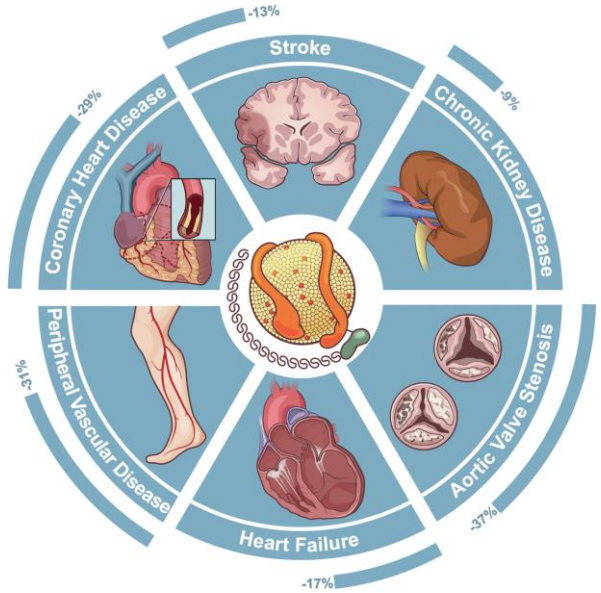


Schmidt et al JLR 2016;57:1339-59



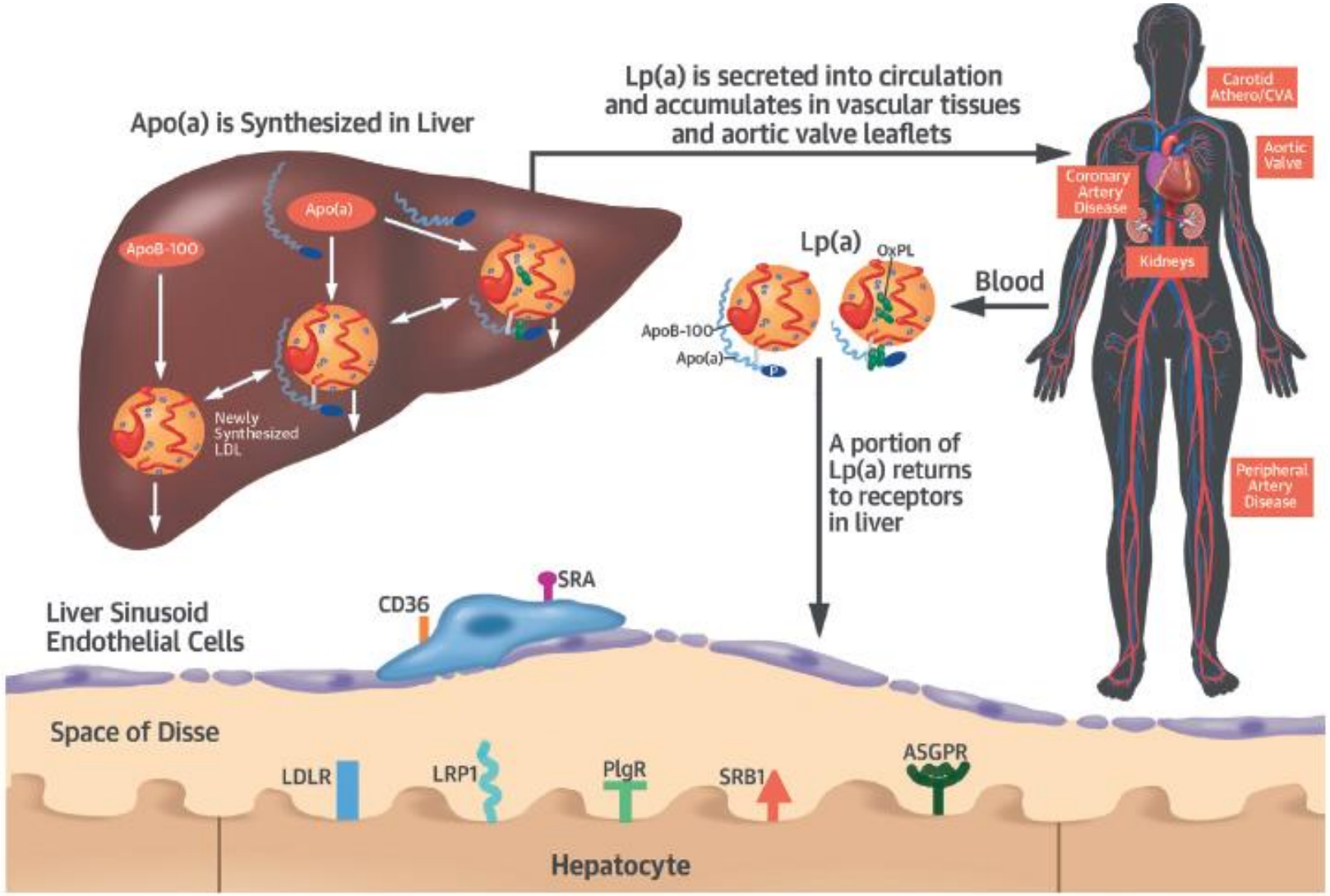
There are over 40 isoforms of Lp(a) ranging from 1 to > 40 KIV_2 repeats.

Tsimikas JACC 2017;69:692-711



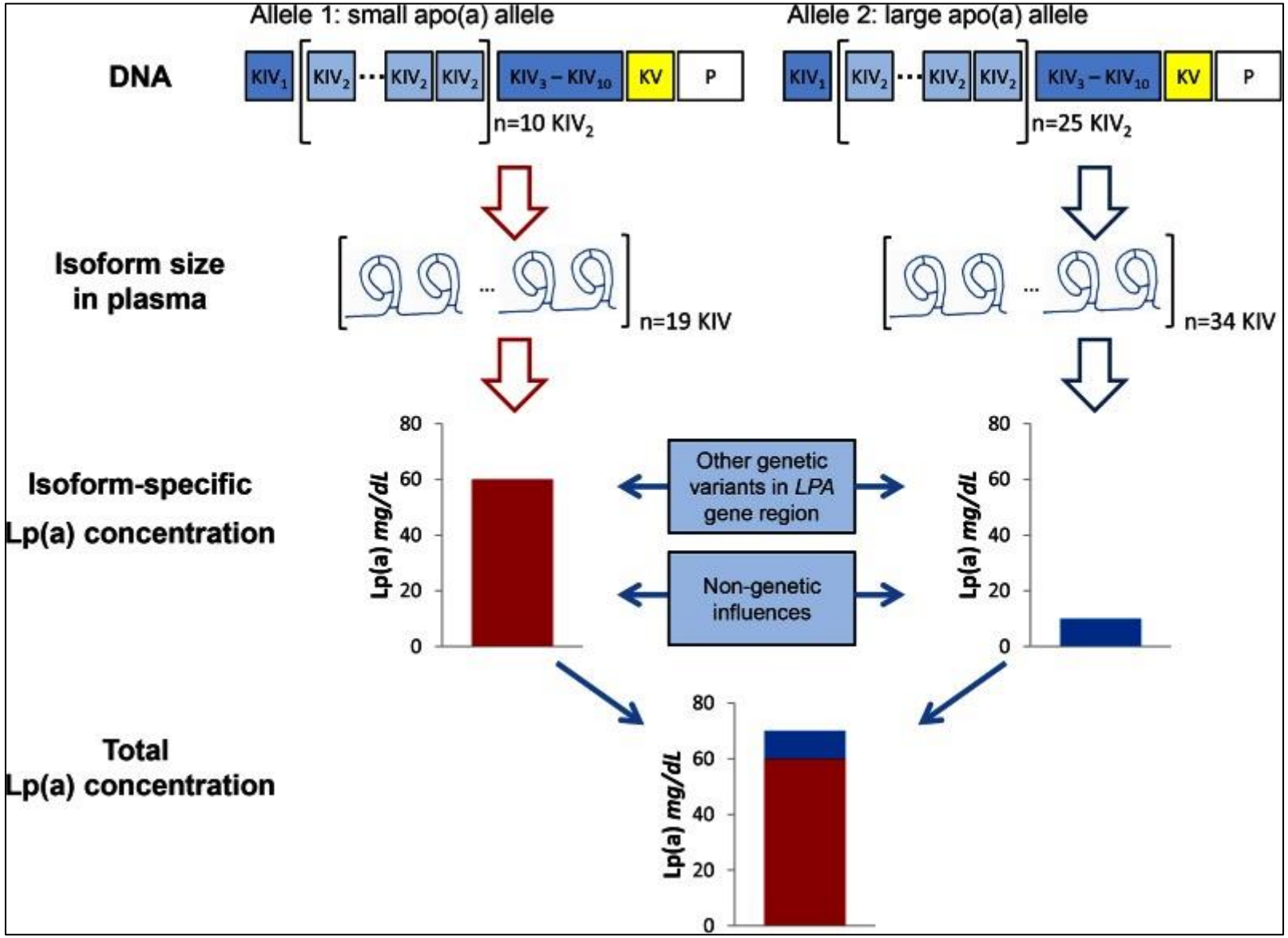
Emdin et al JACC 2016;68:2761-72

Lp(a) Metabolism



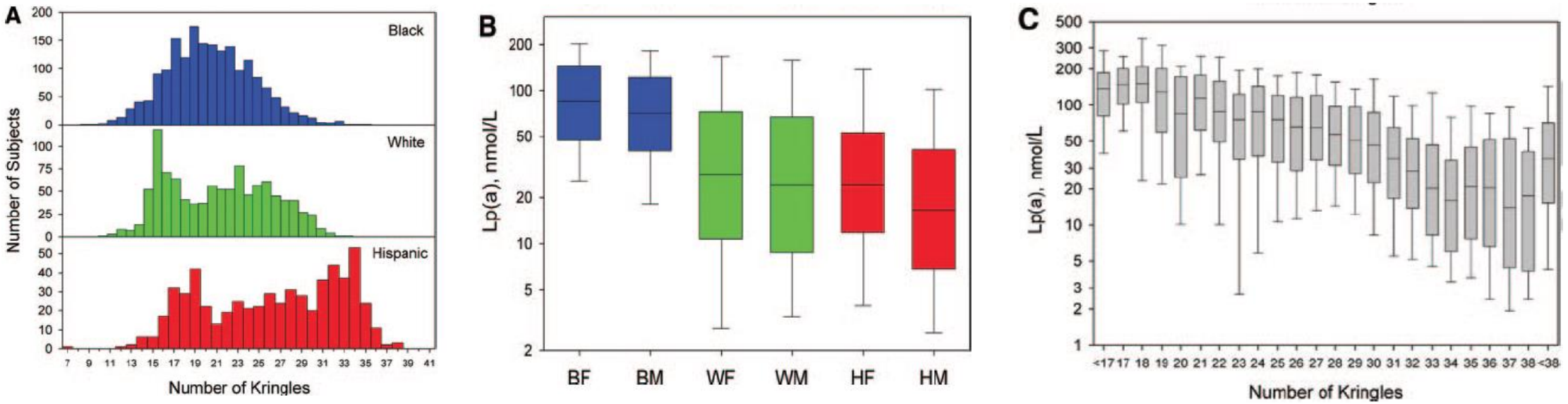
Tsimikas et al JACC 2018;71:177-192

Determination of Lp(a) plasma levels by *LPA* gene variation



Schmidt et al JLR 2016;57:1339-59

Relationship of Apo(a) Isoform Size to Lp(a) Levels in Black, White, and Hispanic Subjects in Dallas Heart Study

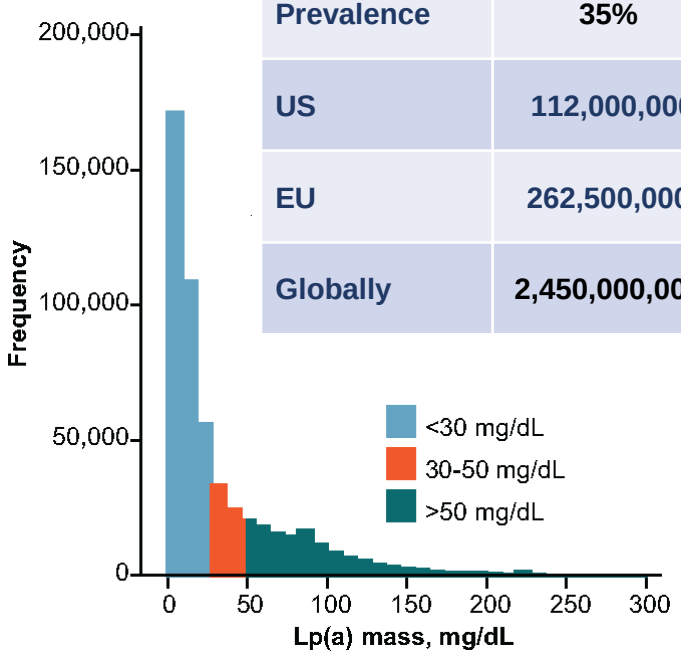


Tsimikas et al Circ 2009;119:1711-1719

Prevalence of Lp(a) Levels in United States and, by Inference, Globally

Data derived from a US laboratory Database in 531,144 patients

Lp(a) distribution in general population extrapolated from the graph					
Lp(a) levels	>30 mg/dL	>60 mg/dL	>90 mg/dL	>116 mg/dL	>180 mg/dL
Prevalence	35%	20%	10%	5%	1%
US	112,000,000	64,000,000	32,000,000	16,000,000	3,200,000
EU	262,500,000	150,000,000	75,000,000	37,500,000	7,500,000
Globally	2,450,000,000	1,400,000,000	700,000,000	350,000,000	70,000,000



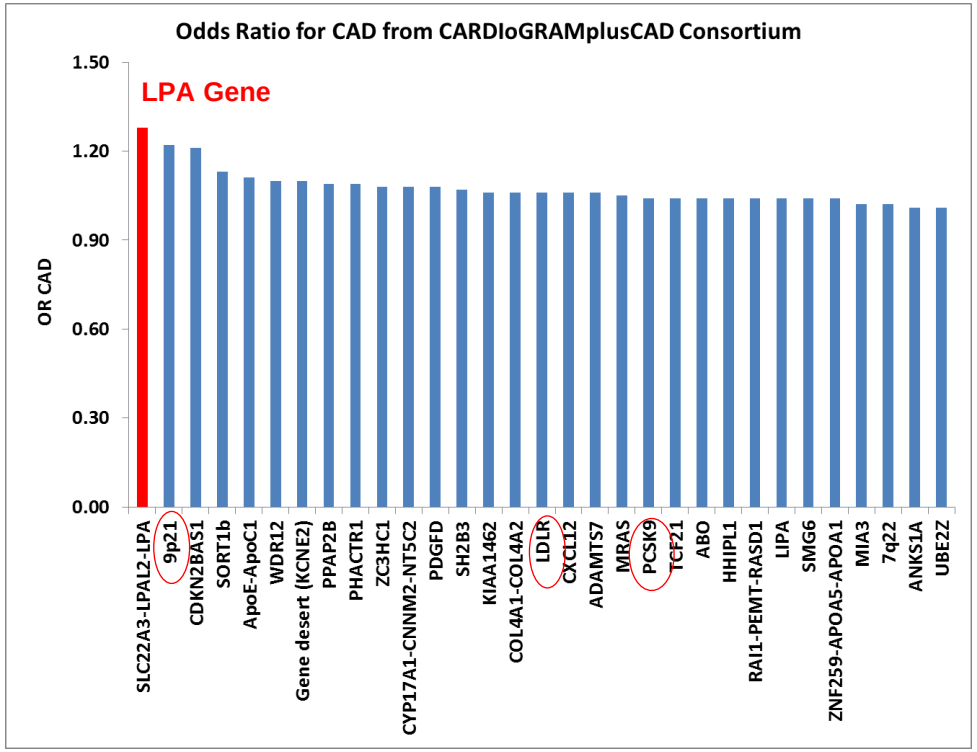
Estimated prevalence assumes 320 million in US, 750 million in EU and 7 billion globally

Varvel et al. Arterioscler Thromb Vasc Biol 2016;36:2239-45.

Genetic Determinants of CAD

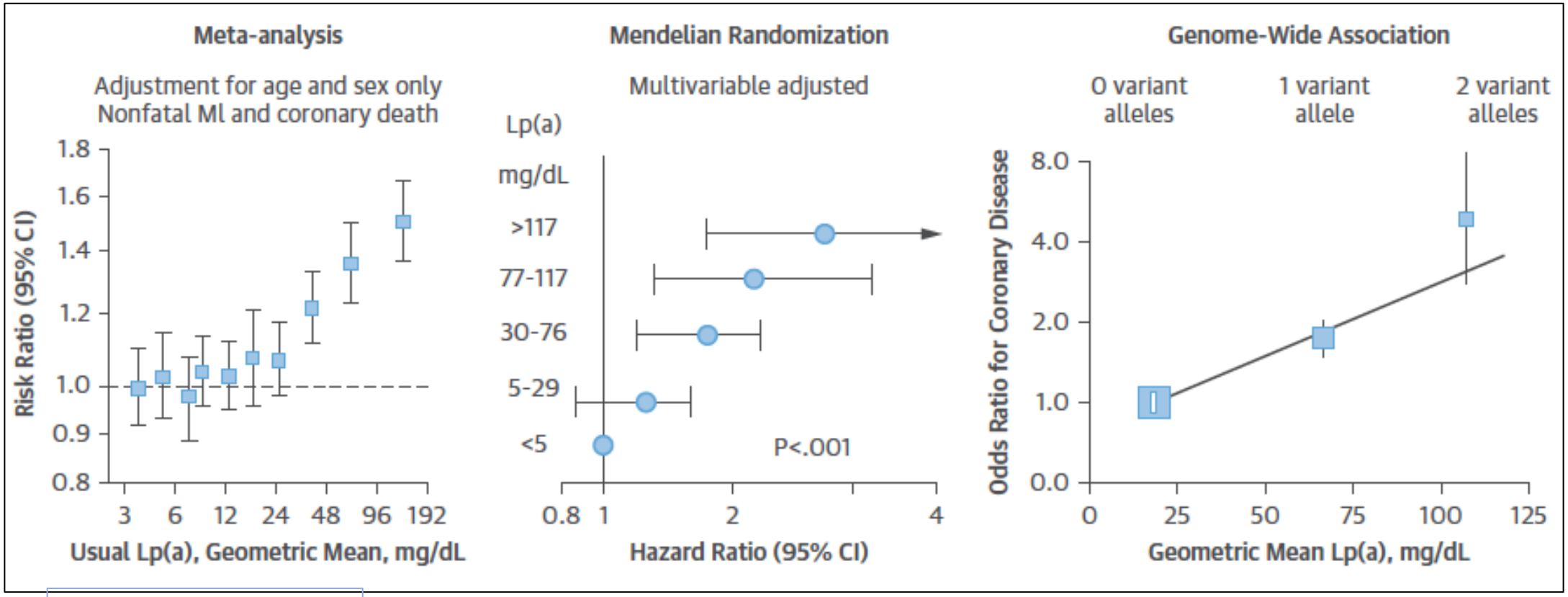
63,746 cases/130,681 controls - 46 loci and 104 independent variants for CAD

The most significant are genes involved in lipid metabolism and inflammation



Elevated Lp(a) Causally Mediates CVD

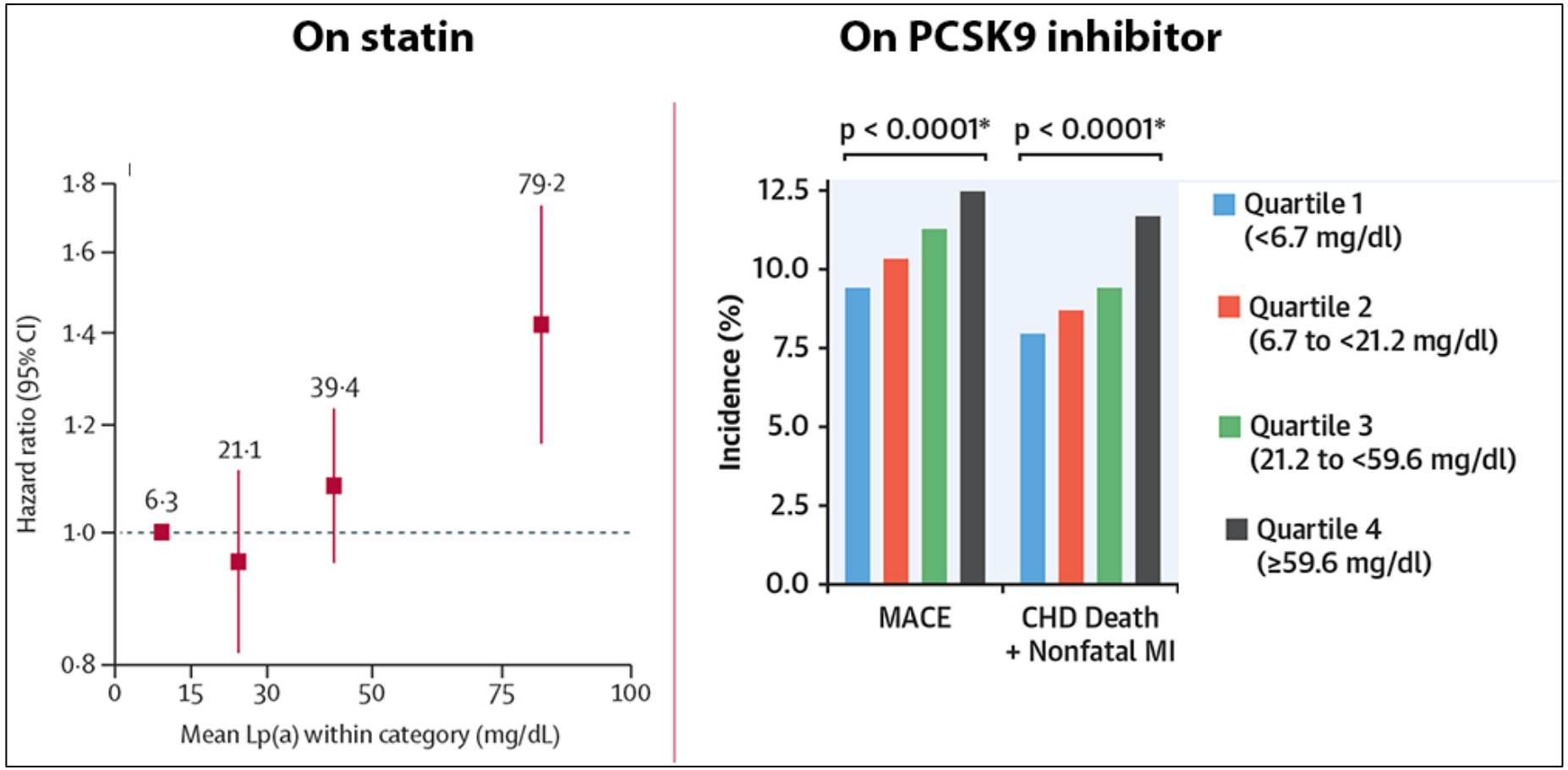
Primary Care Settings



1.3 million patient-yrs

Tsimikas JACC 2017;69:692-711

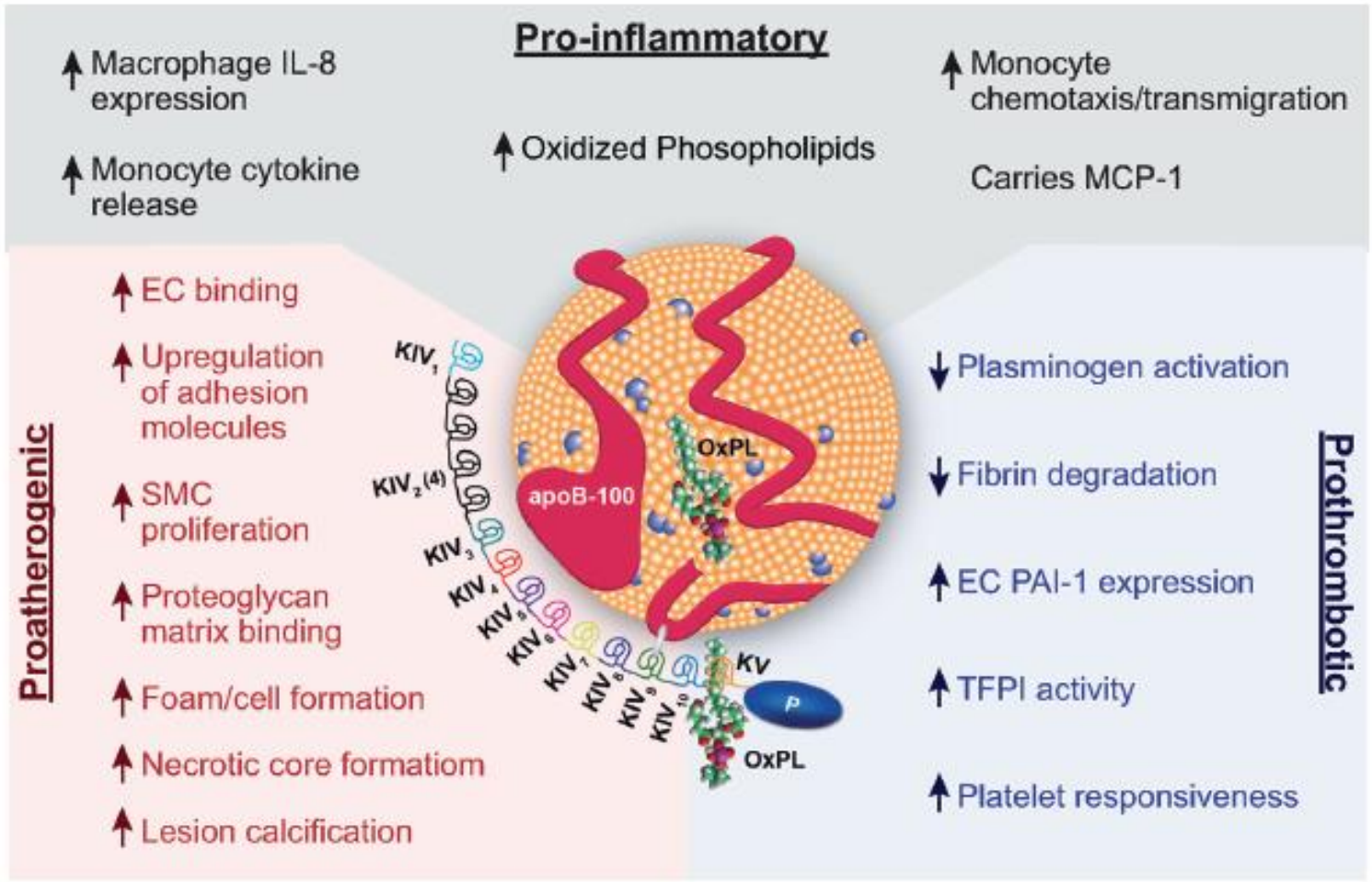
Elevated Lp(a) is Associated with CVD Events in Patients on Statins and PCSK9 Inhibitors



Willeit et al. Lancet 2018;392:1311-20

Bittner VA et al. Am Coll Cardiol. 2020;75:133-144

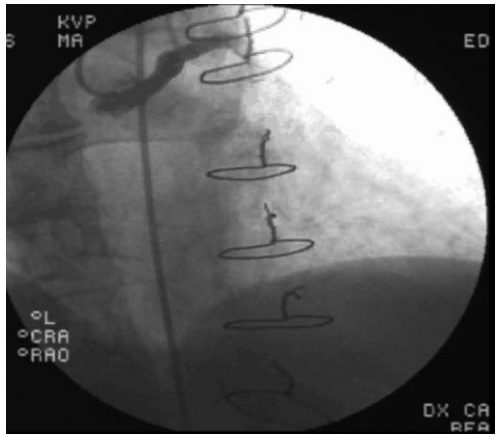
What are the mechanisms through which Lpa) mediates CVD and Aortic Stenosis?



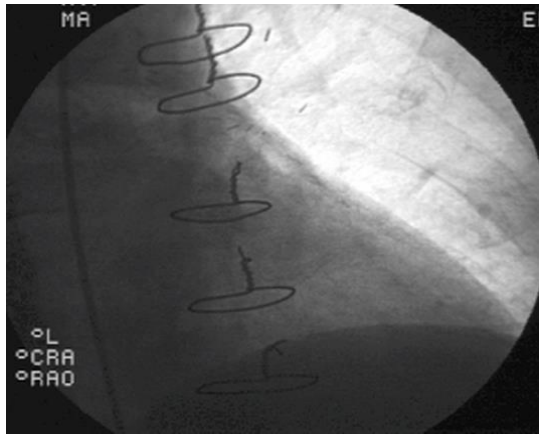
Tsimikas JACC 2017;69:692-711

Lp(a)-OxPL are present in advanced atherosclerotic lesions

Initial Angiogram

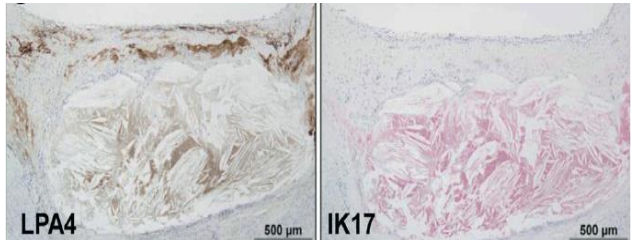


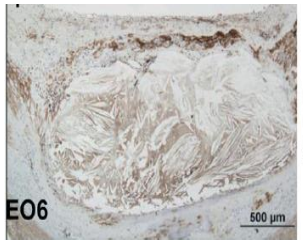
Post stent with distal protection device

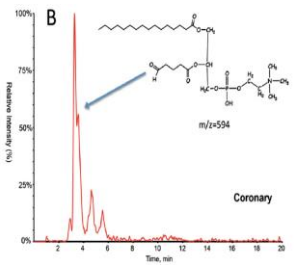


Atheroma Debris

Lp(a)	OxLDL	OxPL	LC-MS/MS of POVPC



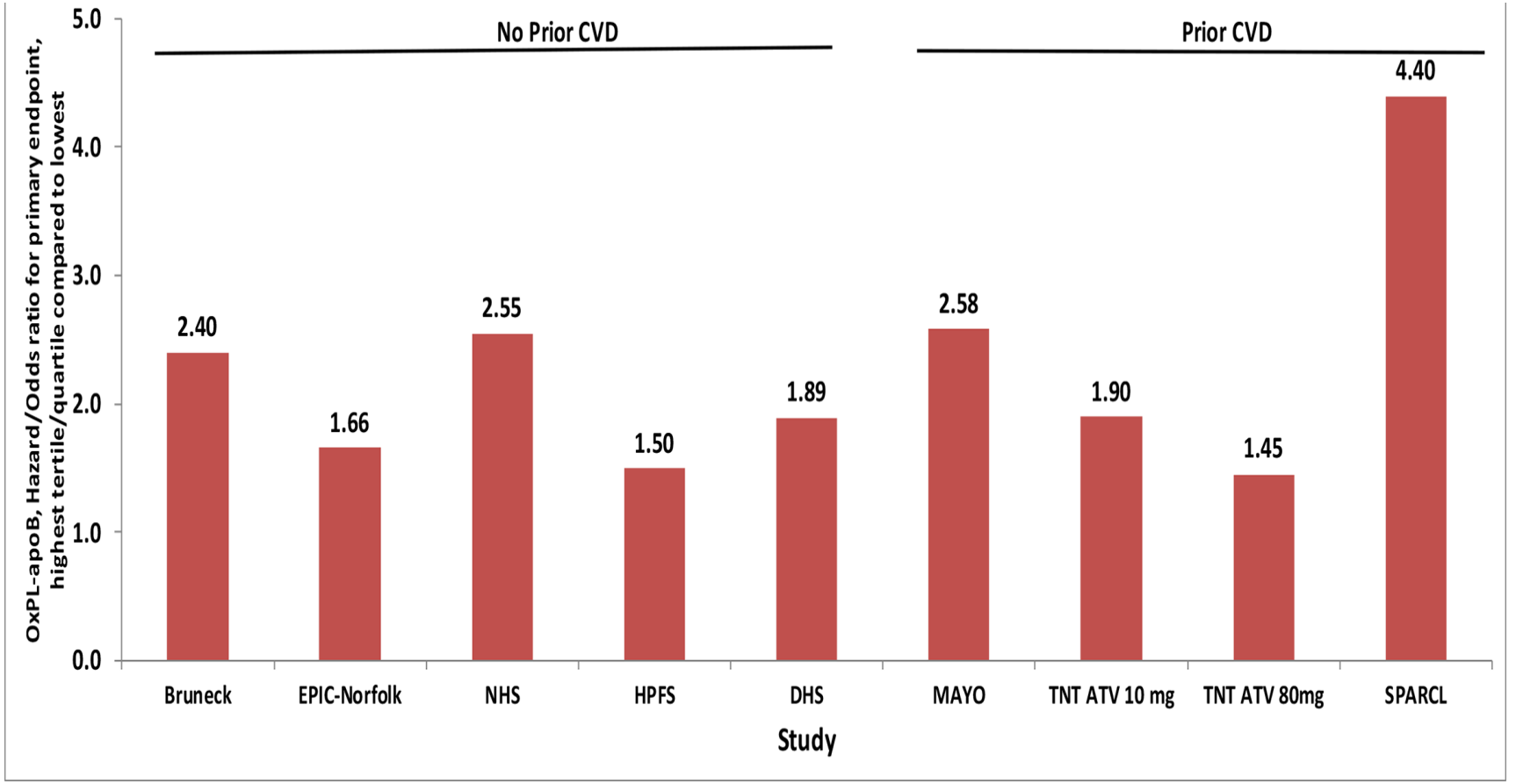




van Dijk RA et al. *J Lipid Res*. 2012;53:2773-90, Ravandi A et al *J Am Coll Cardiol*. 2014;63:1961-71

OxPL-apoB Levels and CVD Outcomes

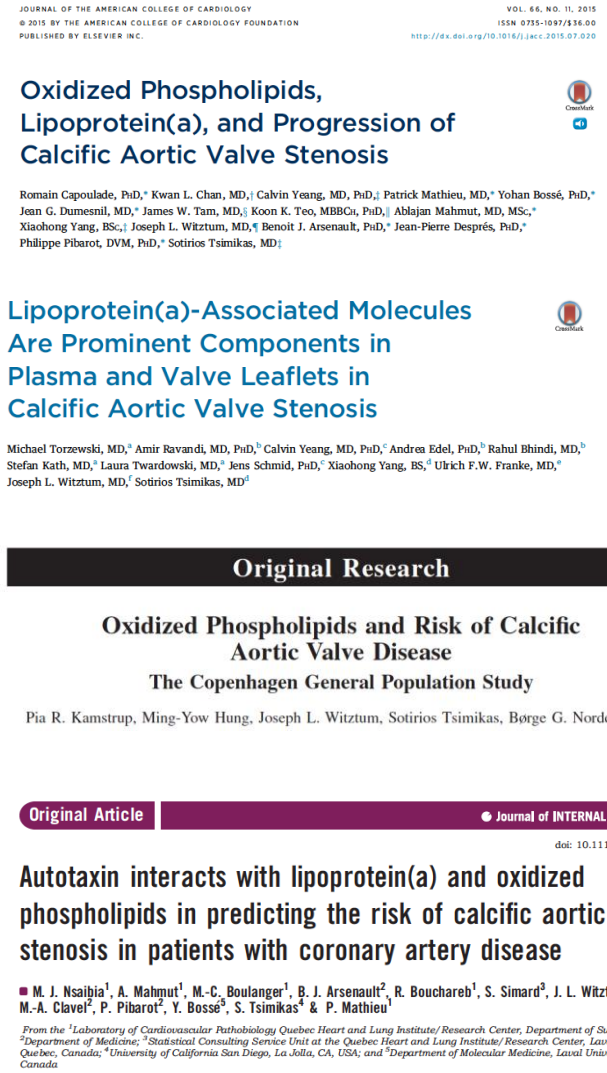
HR/ORs for CAD, PAD, CVA compared to lowest levels



OxPL-apoB is now available for clinical use at Boston Heart Diagnostics

Association of Aortic stenosis and Lp(a)-OxPL

Seven Recent Studies



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Oxidized Phospholipids, Lipoprotein(a), and Progression of Calcific Aortic Valve Stenosis

Romain Capoulade, PhD,* Kwan L. Chan, MD,† Calvin Yeang, MD, PhD,‡ Patrick Mathieu, MD,* Yohan Bossé, PhD,* Jean G. Dumesnil, MD,* James W. Tam, MD,§ Koon K. Teo, MBBCh, PhD,‖ Ablajan Mahmut, MD, MSc,* Xiaohong Yang, BSc,‡ Joseph L. Witztum, MD,¶ Benoit J. Arsenault, PhD,* Jean-Pierre Després, PhD,* Philippe Pibarot, DVM, PhD,* Sotirios Tsimikas, MD†

Lipoprotein(a)-Associated Molecules Are Prominent Components in Plasma and Valve Leaflets in Calcific Aortic Valve Stenosis

Michael Torzewski, MD,[a] Amir Ravandi, MD, PhD,[b] Calvin Yeang, MD, PhD,[c] Andrea Edel, PhD,[b] Rahul Bhindi, MD,[b] Stefan Kath, MD,[a] Laura Twardowski, MD,[a] Jens Schmid, PhD,[c] Xiaohong Yang, BS,[d] Ulrich F.W. Franke, MD,[e] Joseph L. Witztum, MD,[f] Sotirios Tsimikas, MD[d]

Original Research

Oxidized Phospholipids and Risk of Calcific Aortic Valve Disease

The Copenhagen General Population Study

Pia R. Kamstrup, Ming-Yow Hung, Joseph L. Witztum, Sotirios Tsimikas, Børge G. Nordestgaard

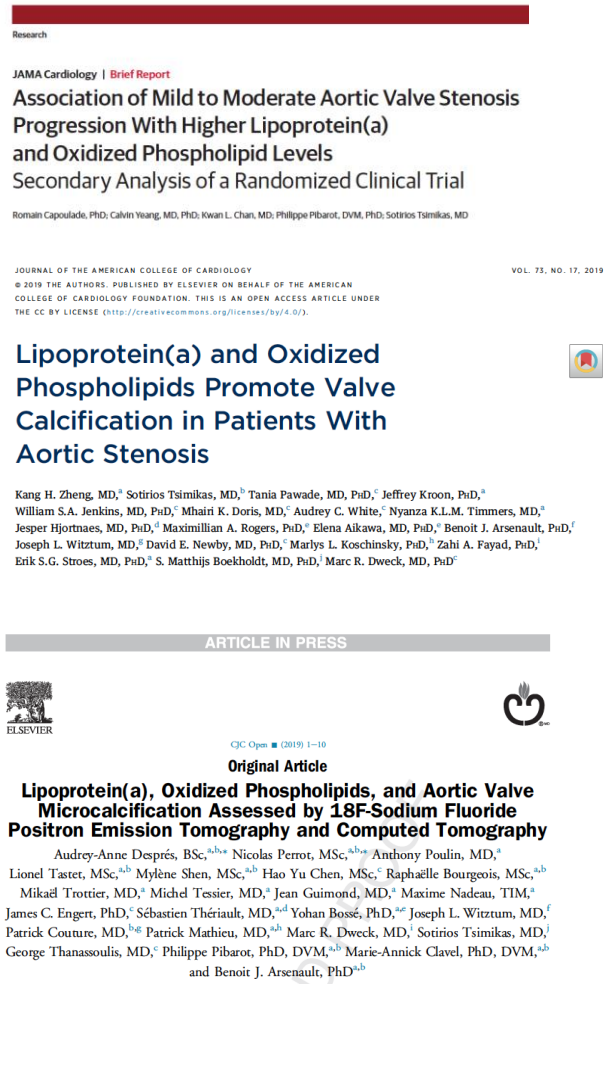
Original Article | Journal of INTERNAL MEDICINE

doi: 10.1111/joim.12519

Autotaxin interacts with lipoprotein(a) and oxidized phospholipids in predicting the risk of calcific aortic valve stenosis in patients with coronary artery disease

M. J. Nsaibia[1], A. Mahmut[1], M.-C. Boulanger[1], B. J. Arsenault[2], R. Bouchareb[1], S. Simard[3], J. L. Witztum[4], M.-A. Clavel[2], P. Pibarot[2], Y. Bossé[5], S. Tsimikas[4] & P. Mathieu[1]

From the [1]Laboratory of Cardiovascular Pathobiology Quebec Heart and Lung Institute/Research Center, Department of Surgery; [2]Department of Medicine; [3]Statistical Consulting Service Unit at the Quebec Heart and Lung Institute/Research Center, Laval University, Quebec, Canada; [4]University of California San Diego, La Jolla, CA, USA; and [5]Department of Molecular Medicine, Laval University, Quebec, Canada



Research

JAMA Cardiology | Brief Report

Association of Mild to Moderate Aortic Valve Stenosis Progression With Higher Lipoprotein(a) and Oxidized Phospholipid Levels

Secondary Analysis of a Randomized Clinical Trial

Romain Capoulade, PhD; Calvin Yeang, MD, PhD; Kwan L. Chan, MD; Philippe Pibarot, DVM, PhD; Sotirios Tsimikas, MD

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VOL. 73, NO. 17, 2019

Lipoprotein(a) and Oxidized Phospholipids Promote Valve Calcification in Patients With Aortic Stenosis

Kang H. Zheng, MD,[a] Sotirios Tsimikas, MD,[b] Tania Pawade, MD, PhD,[c] Jeffrey Kroon, PhD,[a] William S.A. Jenkins, MD, PhD,[c] Mhairi K. Doris, MD,[c] Audrey C. White,[c] Nyanza K.L.M. Timmers, MD,[a] Jesper Hjortnaes, MD, PhD,[d] Maximillian A. Rogers, PhD,[e] Elena Aikawa, MD, PhD,[e] Benoit J. Arsenault, PhD,[f] Joseph L. Witztum, MD,[g] David E. Newby, MD, PhD,[c] Marlys L. Koschinsky, PhD,[h] Zahi A. Fayad, PhD,[i] Erik S.G. Stroes, MD, PhD,[a] S. Matthijs Boekholdt, MD, PhD,[j] Marc R. Dweck, MD, PhD[c]

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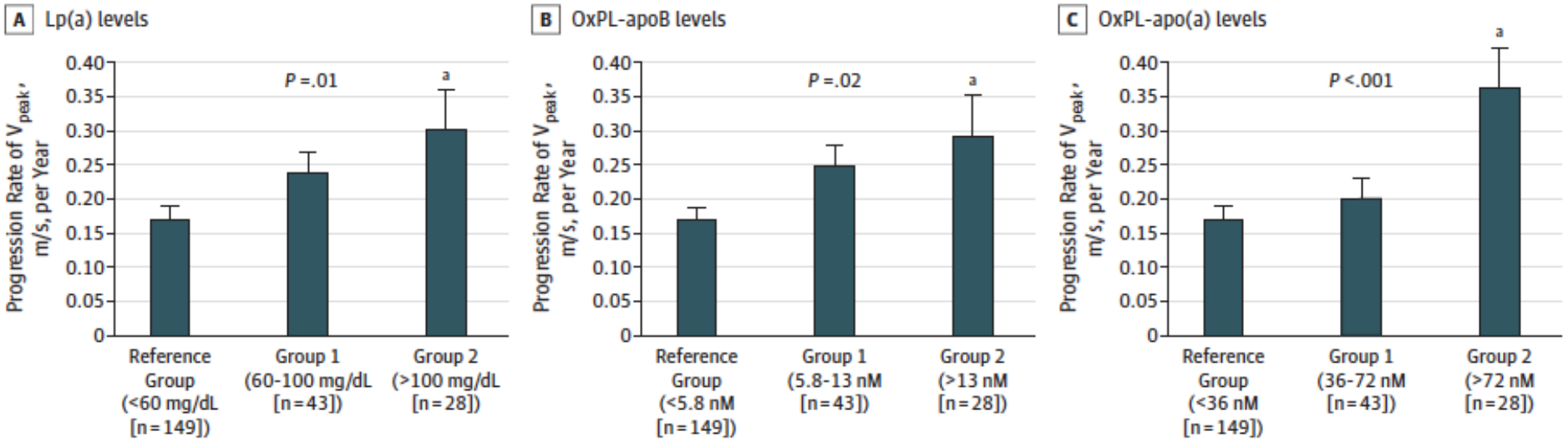
CJC Open ■ (2019) 1–10

Original Article

Lipoprotein(a), Oxidized Phospholipids, and Aortic Valve Microcalcification Assessed by 18F-Sodium Fluoride Positron Emission Tomography and Computed Tomography

Audrey-Anne Després, BSc,[a,b,c] Nicolas Perrot, MSc,[a,b,c] Anthony Poulin, MD,[a] Lionel Tastet, MSc,[a,b] Mylène Shen, MSc,[a,b] Hao Yu Chen, MSc,[c] Raphaëlle Bourgeois, MSc,[a,b] Mikaël Trottier, MD,[a] Michel Tessier, MD,[a] Jean Guimond, MD,[a] Maxime Nadeau, TIM,[a] James C. Engert, PhD,[c] Sébastien Thériault, MD,[a,d] Yohan Bossé, PhD,[a,e] Joseph L. Witztum, MD,[f] Patrick Couture, MD,[b,g] Patrick Mathieu, MD,[a,b] Marc R. Dweck, MD,[i] Sotirios Tsimikas, MD,[j] George Thanassoulis, MD,[c] Philippe Pibarot, PhD, DVM,[a,b] Marie-Annick Clavel, PhD, DVM,[a,b] and Benoit J. Arsenault, PhD[a,b]

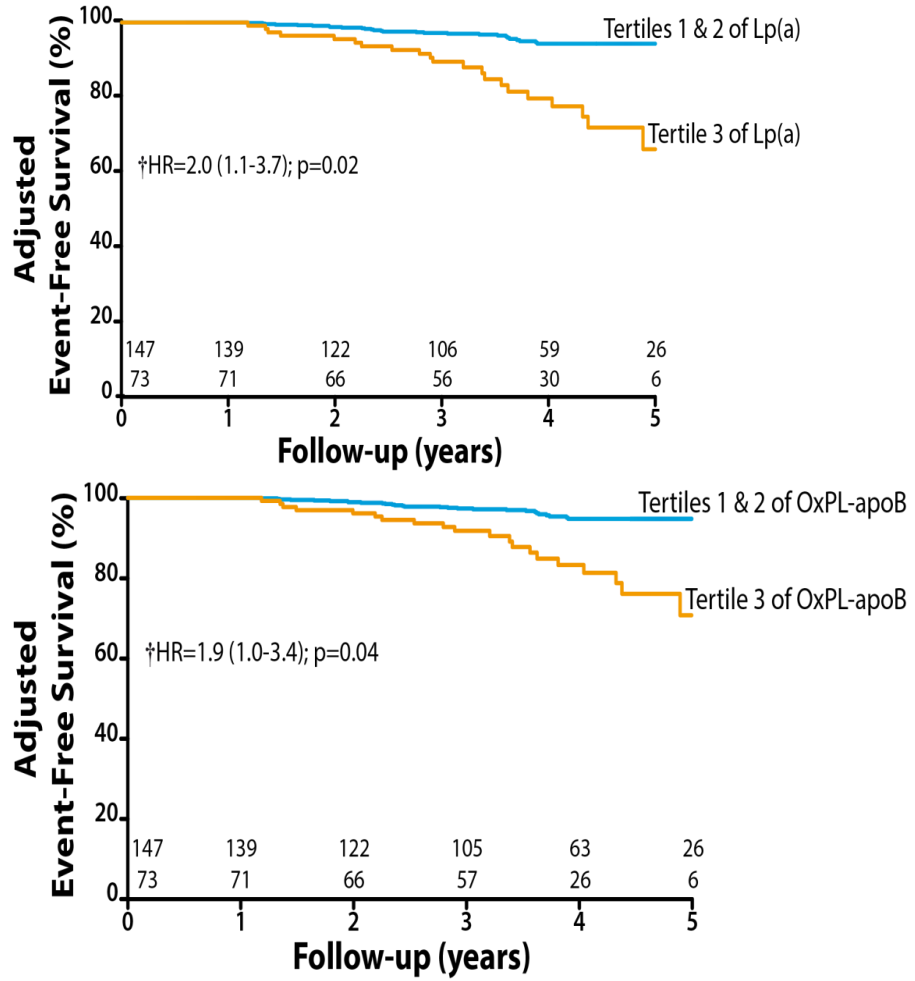
Progression of aortic stenosis according to Lp(a) and OxPL levels



1/3rd of patients with aortic stenosis have elevated Lp(a)

Capoulade et al JAMA Cardiol 2018;3:1212-1217

Elevated Lp(a) and OxPL-apoB Predict the Need for AVR



Models adjusted for age, male gender and baseline V_{peak}

Capoulade et al JAMA Cardiol 2018;3:1212-1217

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Lp(a): Testing and Current Role in Guidelines and Risk Assessment

Sotirios Tsimikas, MD
Director of Vascular Medicine
Professor of Medicine
University of California San Diego

Clinical Lp(a) assays

- **Lp(a) mass -- normal <30 mg/dL**
  - Measures apo(a), apoB, cholesterol, cholesteryl esters, triglycerides, phospholipids and carbohydrates
  - Not traceable to a reference system
- **Lp(a) molar concentration -- normal <75 nmol/L**
  - Detects apo(a) only
  - Traceable to a WHO/IFCC reference material
- **Lp(a)-Cholesterol -- normal <10 mg/dL**
  - not validated clinically

Table 1 Ratios of Lp(a) molar concentration (nmol/L) to Lp(a) mass (mg/dL)

Lp(a) concentration (nmol/L)	#Samples	Mean (SD)/median (IQR) NLMDRL/UCSD ratio
All levels	1635	2.42 (1.25)/2.30 (1.63–3.02)
<75	494	1.82 (1.44)/1.54 (1.10–2.22)
75–<125	296	2.32 (1.31)/2.07 (1.63–2.64)
125–<175	239	2.33 (0.76)/2.24 (1.77–2.71)
175–<225	242	2.62 (0.97)/2.49 (2.06–3.02)
225–<275	127	2.80 (0.67)/2.76 (2.30–3.16)
275–<325	70	3.00 (0.58)/2.93 (2.55–3.35)
≥325	167	3.64 (0.78)/3.45 (3.09–4.03)

LP(a), lipoprotein(a); NLMDRL, Northwest Lipid Metabolism and Diabetes Research Laboratories; UCSD, University of California, San Diego.

Tsimikas et al *J Clin Lipidol*. 2018;12:1313-23

Conditions Affecting Plasma Lp(a) Levels

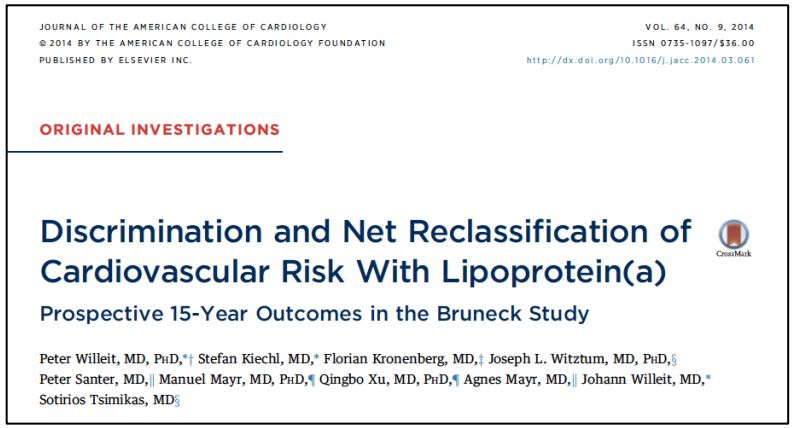
Increase

- FH
- Familial defective apolipoprotein B-100
- Pregnancy
- Acute phase response (ACS)
- Inflammation
- Rheumatologic conditions (RA, Lupus)
- Post menopausal state
- Hypothyroidism
- Growth hormone
- Chronic renal failure
- Nephrotic syndrome

Decrease

- Hyperthyroidism
- Severe sepsis
- Estrogens, testosterone
- Biliary obstruction
- Severe liver disease
- Abetalipoproteinaemia
- Lecithin-cholesterol acyltransferase (LCAT) deficiency
- Lipoprotein lipase (LPL) deficiency
- Severe hypertriglyceridemia

Can measuring Lp(a) reclassify risk?



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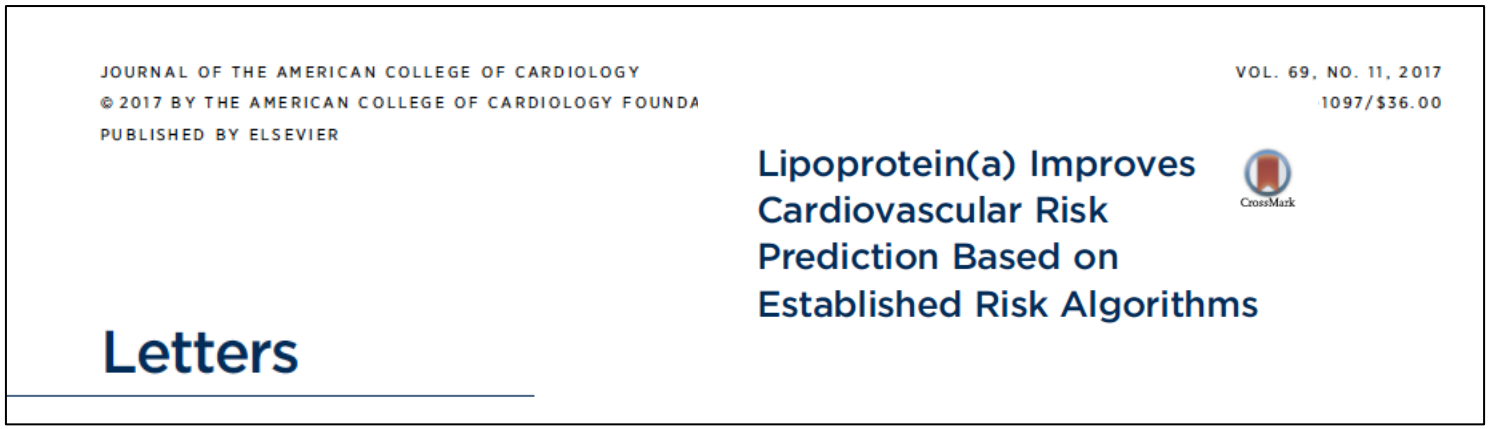
ORIGINAL INVESTIGATIONS

Discrimination and Net Reclassification of Cardiovascular Risk With Lipoprotein(a)

Prospective 15-Year Outcomes in the Bruneck Study

Peter Willeit, MD, PhD,*† Stefan Kiechl, MD,* Florian Kronenberg, MD,‡ Joseph L. Witztum, MD, PhD,§ Peter Santer, MD,‖ Manuel Mayr, MD, PhD,¶ Qingbo Xu, MD, PhD,¶ Agnes Mayr, MD,‖ Johann Willeit, MD,* Sotirios Tsimikas, MD§

Willeit JACC. 2014;64:851-60



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VOL. 69, NO. 11, 2017
1097/$36.00

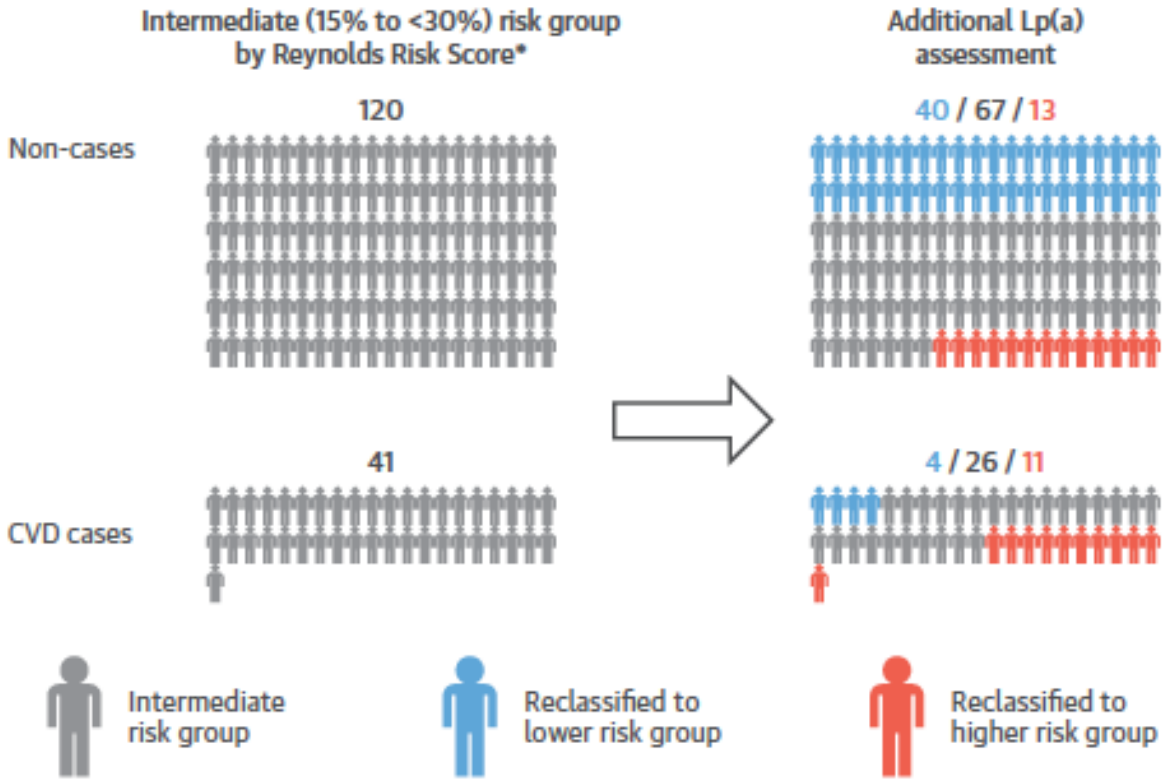
Lipoprotein(a) Improves Cardiovascular Risk Prediction Based on Established Risk Algorithms

Letters

Verbeek et al JACC 2017;69:1513-15

Lp(a) and Reclassification of Risk

Measuring Lp(a) changes risk category in 4/10 patients



The addition of Lp(a) to these risk scores allowed reclassification of 39.6% of individual into either lower or higher risk categories depending on the Lp(a) level

Willeit et al JACC 2014;64:851-60

Lp(a) Guidelines - 7 Guidelines Recommend Lp(a) Testing

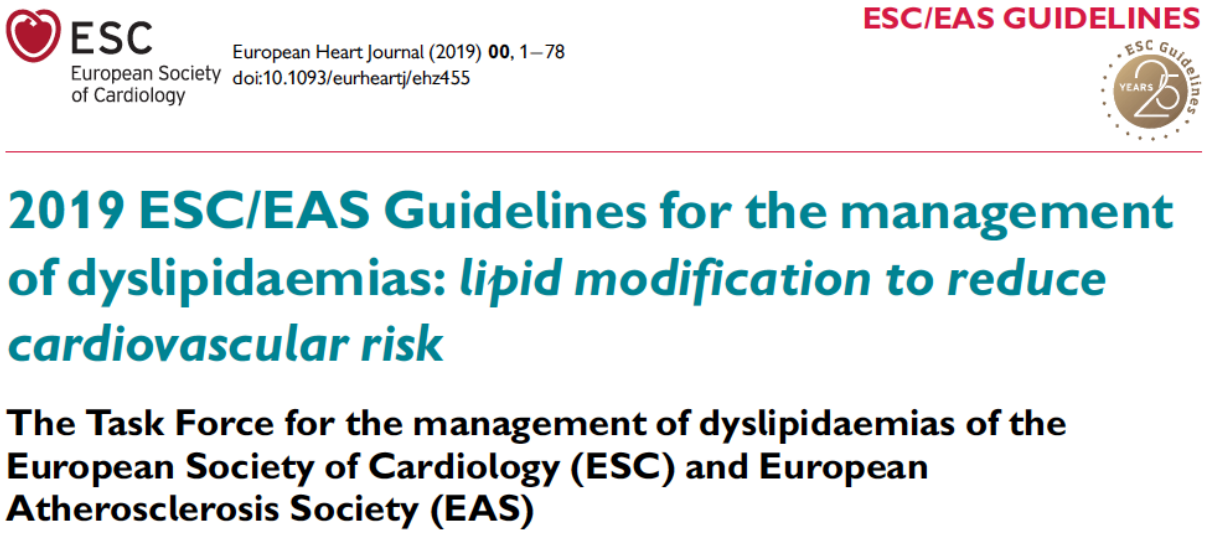
EAS/ESC and Canadian Guidelines recommend every adult have at least 1 Lp(a) levels checked in their lifetime

Guideline	Authors	Year	Lp(a) risk thresholds
Canadian Cardiovascular Society	Anderson et al.	2016	> 30 mg/dL
American Society of Apheresis	Stefanutti et al.	2017	> 30 mg/dl (> 45 nmol/L)
ACC/ AHA Task force on Clinical Practice Guidelines	Grundy et al.	2019	>50 mg/dL (>125n mol/L)
ESC and ESA	Mach et al.	2019	Not defined, but the 2016 ESA/ESA guidelines defined it as > 50 mg/dL, based on European population thresholds Lp(a) > 180 mg/dL (> 430 nmol/ L) is defined equivalent for HoFH
NLA	Wilson et al.	2019	> 50 mg/ dL or 100 nmol/ L (based on > 80th population percentile Caucasians)
Heart UK consensus Statement	Cegla et al	2019	Risk thresholds 32-90 nmol/ L minor; 90-200 n mol/ L moderate; 200-400 nmol/ L; high > 400 nmol/ LL very high

Tsimikas S, Stroes ESG. The dedicated "Lp(a) clinic": A concept whose time has arrived? *Atherosclerosis*. 2020;300:1-9.

ESC/EAS Guidelines 2019

Statement on Lp(a)



"Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia."

Lp(a) ICD-10 code

ICD-10 codes

E78.41 Elevated lipoprotein(a)

Z83.430 Family history of elevated lipoprotein(a)

E78.41 is a billable/specific ICD-10-CM code that can be used to indicate a diagnosis for reimbursement purposes

The 2020 edition of ICD-10-CM E78.41 became effective on October 1, 2019

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Current Treatment Options for Lp(a)

Sotirios Tsimikas, MD
Director of Vascular Medicine
Professor of Medicine
University of California San Diego

Selected Clinically Available Agents or Procedures Affecting Lp(a) Levels

TABLE 1 Selected Clinically Available Agents or Procedures Affecting Lp(a) Levels

Lp(a)-Lowering Therapy	Lp(a) Effect	Possible Mechanism of Lp(a) Lowering	Best Level of Evidence
Lipid apheresis	70% acute, 35% time-averaged reduction	Removal of Lp(a) and other lipoproteins using adsorption columns	Several longitudinal prospective trials (45)
Nicotinic acid	20% to 30% reduction	Inhibition of LPA promoter via cyclic AMP (46)	Randomized control trials (12)
PCSK9 inhibitors	14–30% reduction	Unknown, possibly due to decreased apo(a) secretion	Multiple, large, randomized trials (16,17,47)
Mipomersen	20% to 40% reduction	Inhibits synthesis of apoB-100	4 phase 3 randomized, placebo-controlled trials (24)
Lomitapide	17% reduction	Decrease in VLDL synthesis via microsomal triglyceride transfer protein inhibition	Small phase 2 and 3 randomized, placebo-controlled trials (48)
Statins	8% to 24% increase	Unknown, possibly due to increase in apo(a) secretion via PCSK9 (22)	Large meta-analysis and smaller single studies (22)
Ezetimibe/fibrates/bile acid sequestrants	? neutral	N/A	Small clinical studies, more data needed (49)

apo(a) = apolipoprotein(a); apoB = apolipoprotein B; Lp(a) = lipoprotein(a); N/A = not available; PCSK9 = proprotein convertase subtilisin kexin type 9; VLDL = very low-density lipoprotein.

Tsimikas S, Moriarty PM, Stroes ES. J Am Coll Cardiol. 2021;77:1576-89

Statins increase Lp(a) levels

HMG CoA Reductase Inhibitors Lower LDL Cholesterol Without Reducing Lp(a) Levels

Gerhard M. Kostner, PhD, Dov Gavish, MD, Beate Leopold, PhD, Klaus Bolzano, PhD, Moshe S. Weintraub, MD, and Jan L. Breslow, MD

1316 **Circulation** *Vol 80, No 5, November 1989*

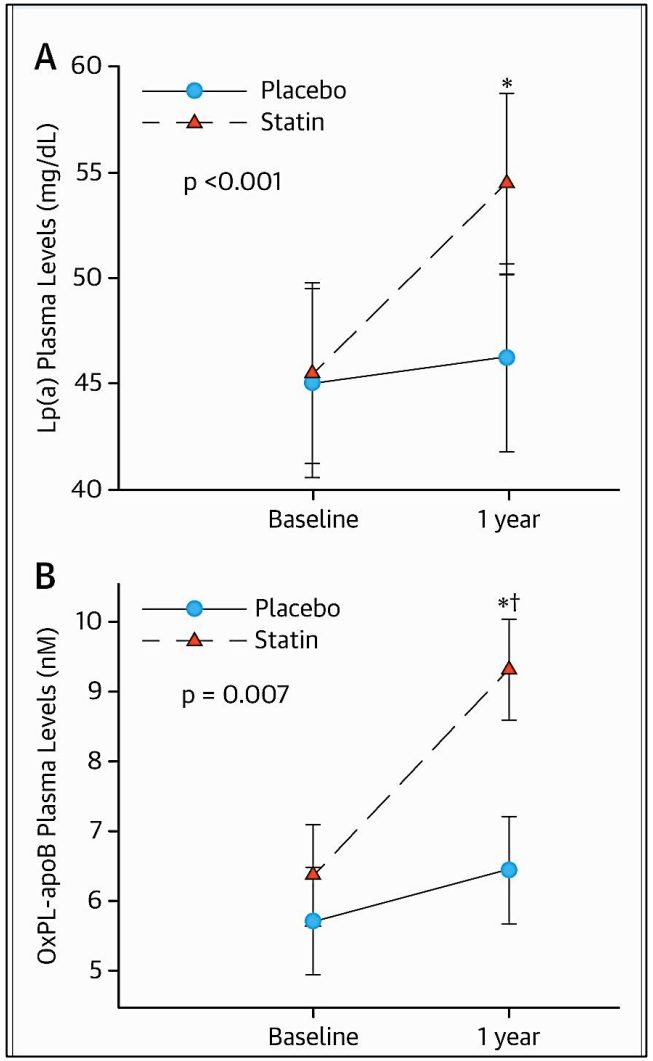
TABLE 2. Effect of Lovastatin Therapy on Lipid and Lipoprotein Levels in 14 Patients With Hypercholesterolemia

Lovastatin (mg/day)	Total cholesterol (mg/dl)	Triglycerides (mg/dl)	Cholesterol (mg/dl)			Lp(a) protein (mg/dl)	% Change in LDL	% Change in Lp(a)
			VLDL	LDL	HDL			
0	391±25	179±21	79±7.3	272±21	48±4	15±6.5	0	0
20	316±19	148±16	48±6.5	211±18	49±4	19±8	−22.8±1.9‡	+27.0±6.3†
40	284±14	132±13	43±5.4	185±17	49.5±2.5	18.5±9	−32.1±2.3‡	+23.0±7.0*
80	245±19	115±10	37±4.3	158±14	48±2.9	21.3±10.3	−43.4±2.2‡	+28.8±4.5‡
80	236±11	121±11	42.5±5	144±9	48±2.9	21.7±10	−46.8±2.7‡	+33.7±6.3‡

Data are mean±SEM.
Therapy lasted for 6 months.
*$p<0.05$, †$p<0.01$, ‡$p<0.005$ by paired t test.

Increase in Lp(a) and OxPL-apoB Levels from Baseline to 1-year with Rosuvastatin in ASTRONOMER

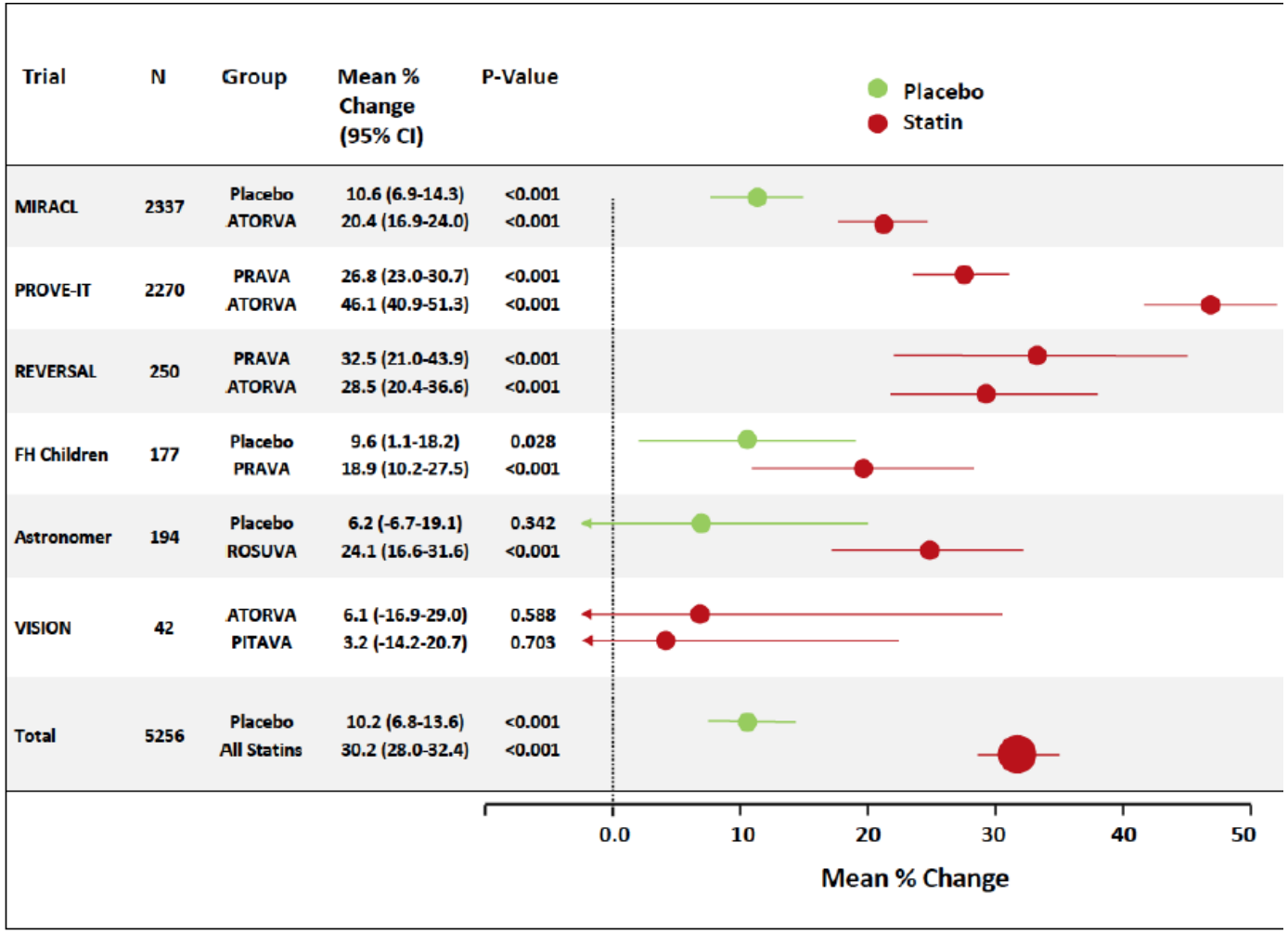
Potential Explanation of the failure of statins in aortic stenosis



Capoulade et al JACC 2015;66:1236-46

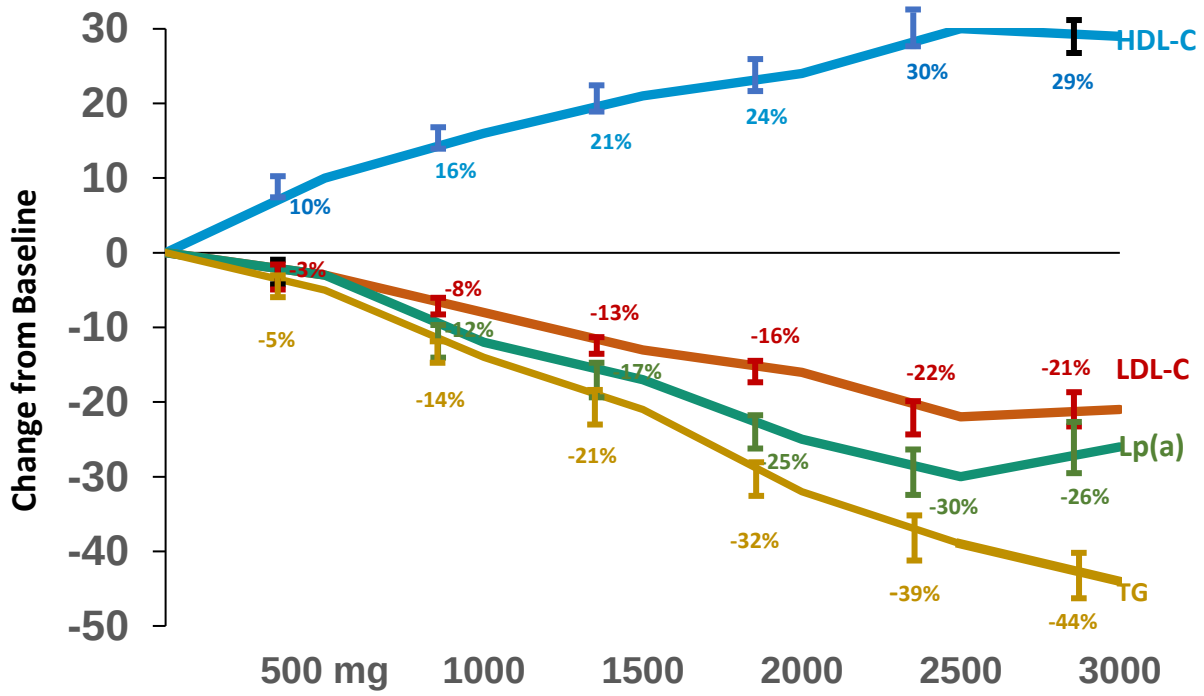
Statins increase Lp(a) levels

Individual-patient meta-analysis of 5256 patients



Tsimikas et al. Eur Heart J. 2020;41:2275-84.

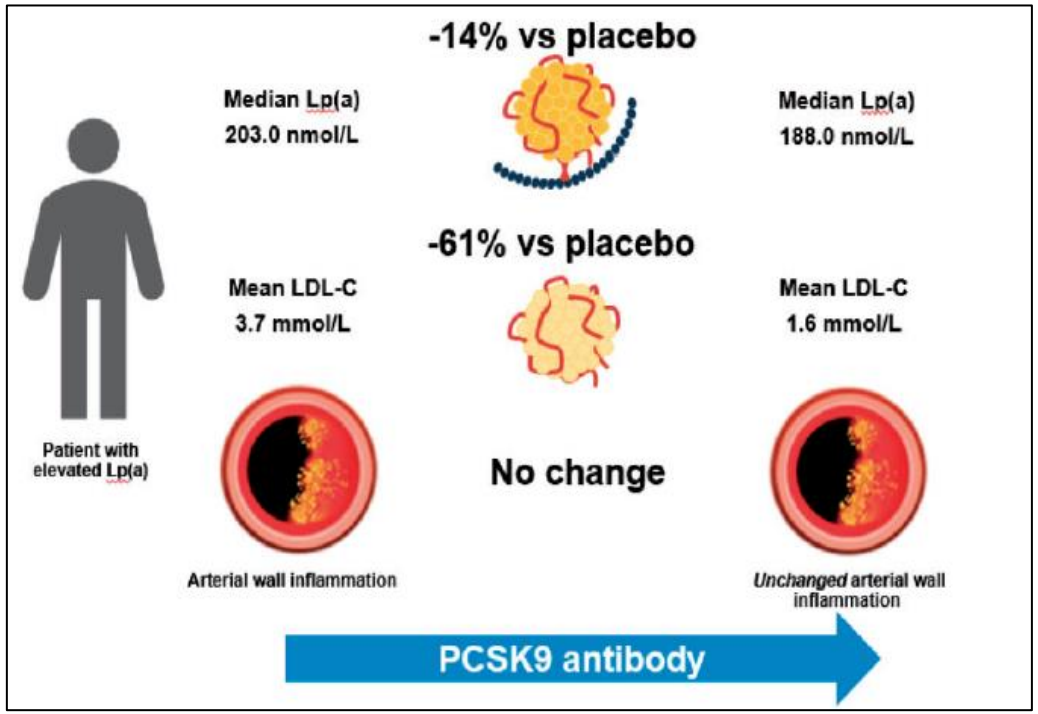
Extended-Release Nicotine Acid

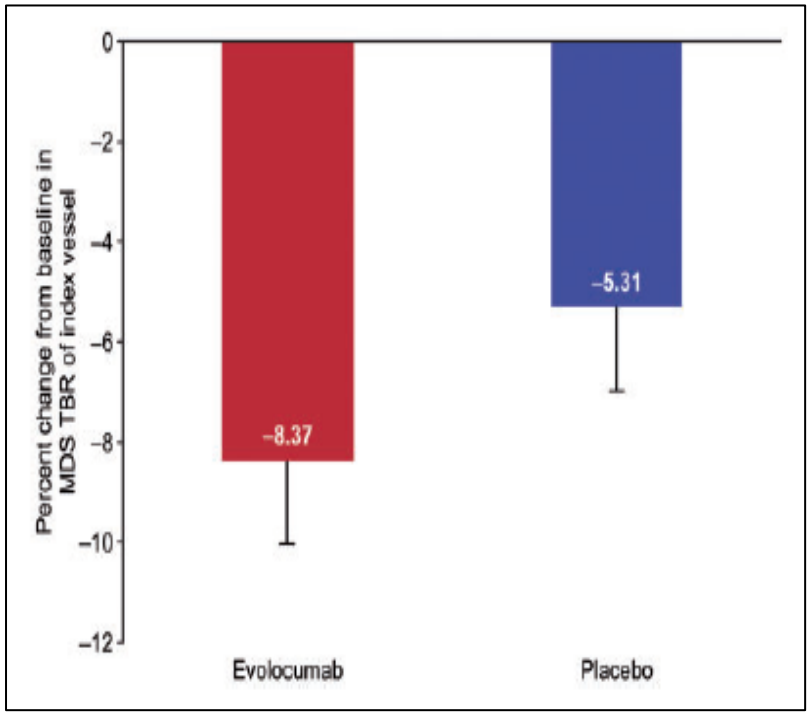


Data from pivotal placebo-controlled studies

PCSK9i is Poorly Effective in Lowering Lp(a) (14%) and Does not Affect Aorta/Carotid ^{18}FDG Uptake

Anitschkow Trial



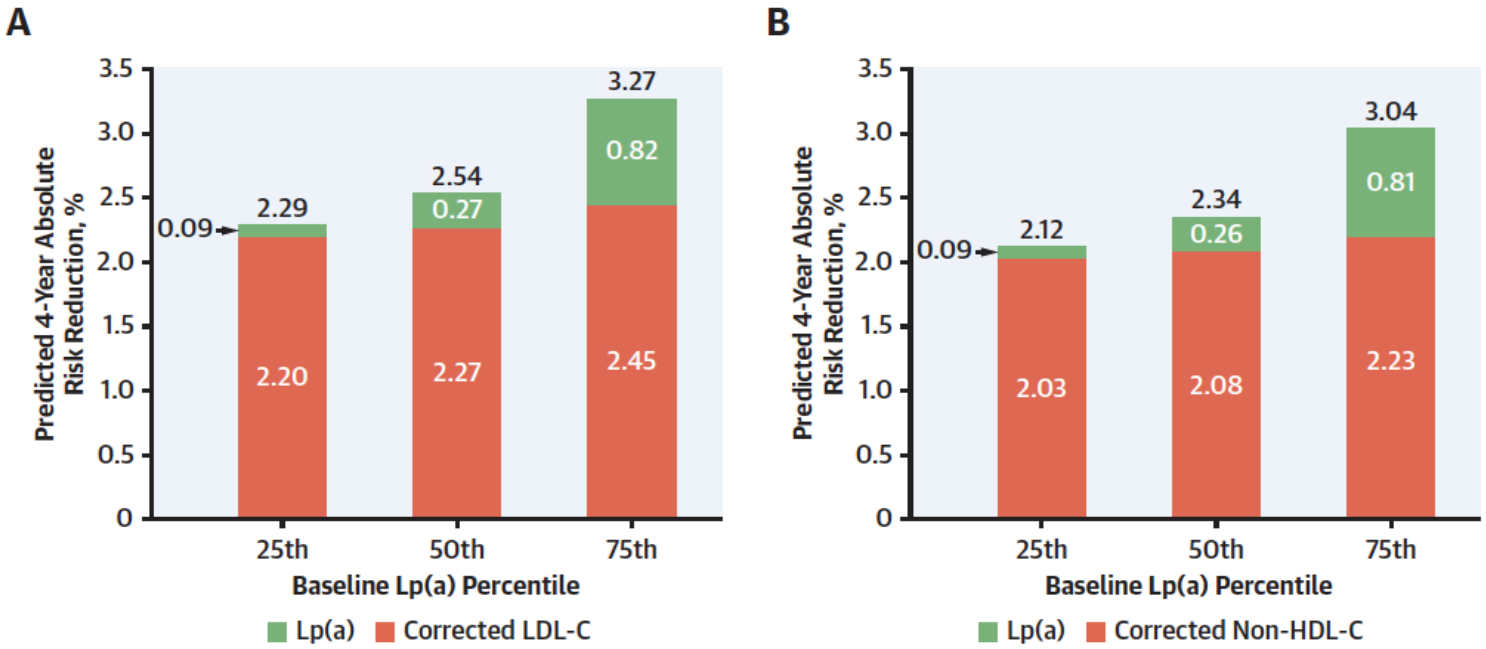


Stiekema et al Eur Heart J 2019;40:2775-81

Reduction in First MACE Events Attributable to Lp(a) Lowering with PCSK9i

ODYSSEY OUTCOMES Trial

CENTRAL ILLUSTRATION Relative Contributions of Changes in Concentrations of Corrected Low-Density Lipoprotein Cholesterol, Corrected Non-High-Density Lipoprotein Cholesterol, and Lipoprotein(a) to the Absolute Reduction in Major Adverse Cardiovascular Events in the Alirocumab Group



Bittner, V.A. et al. J Am Coll Cardiol. 2020;75(2):133–44.

Reduction in Total MACE Events Attributable to Lp(a) Lowering with PCSK9i

ODYSSEY OUTCOMES Trial

Graphical Abstract

Baseline Lp(a) quartile	Month 4 median Lp(a) reduction	HR (95% CI) for Lp(a) median reduction	Joint risk reduction attributable to Lp(a)
Quartile 1 (<6.7 mg/dL)	0 mg/dL	1.00	0%
Quartile 2 (6.7 to <21.2 mg/dL)	5.1 mg/dL	0.975 (0.952, 0.997)	13%
Quartile 3 (21.2 to <59.6 mg/dL)	9.9 mg/dL	0.951 (0.909, 0.995)	23%
Quartile 4 (≥59.6 mg/dL)	20.1 mg/dL	0.903 (0.824, 0.990)	39%
Overall	5.0 mg/dL	0.975 (0.953, 0.997)	13%

Szarek et al Eur Heart J 2020;41:4245-4255

Aspirin and Lp(a)

Polymorphism in the apolipoprotein(a) gene, plasma lipoprotein(a), cardiovascular disease, and low-dose aspirin therapy

Daniel I. Chasman[a,b,*], Dov Shiffman[d], Robert Y.L. Zee[a,b], Judy Z. Louie[d], May M. Luke[d], Charles M. Rowland[d], Joseph J. Catanese[d], Julie E. Buring[a,b], James J. Devlin[d], Paul M. Ridker[a,b,c]

Women's health study – randomized trial ASA 100 mg every other day vs. placebo, healthy women >= 45, no cardiovascular disease, 10 year follow up

- Genotyped 25,131 healthy Caucasian participants for rs3798220 of apolipoprotein(a)
- 486 minor allele carriers assigned to aspirin, 417 to placebo

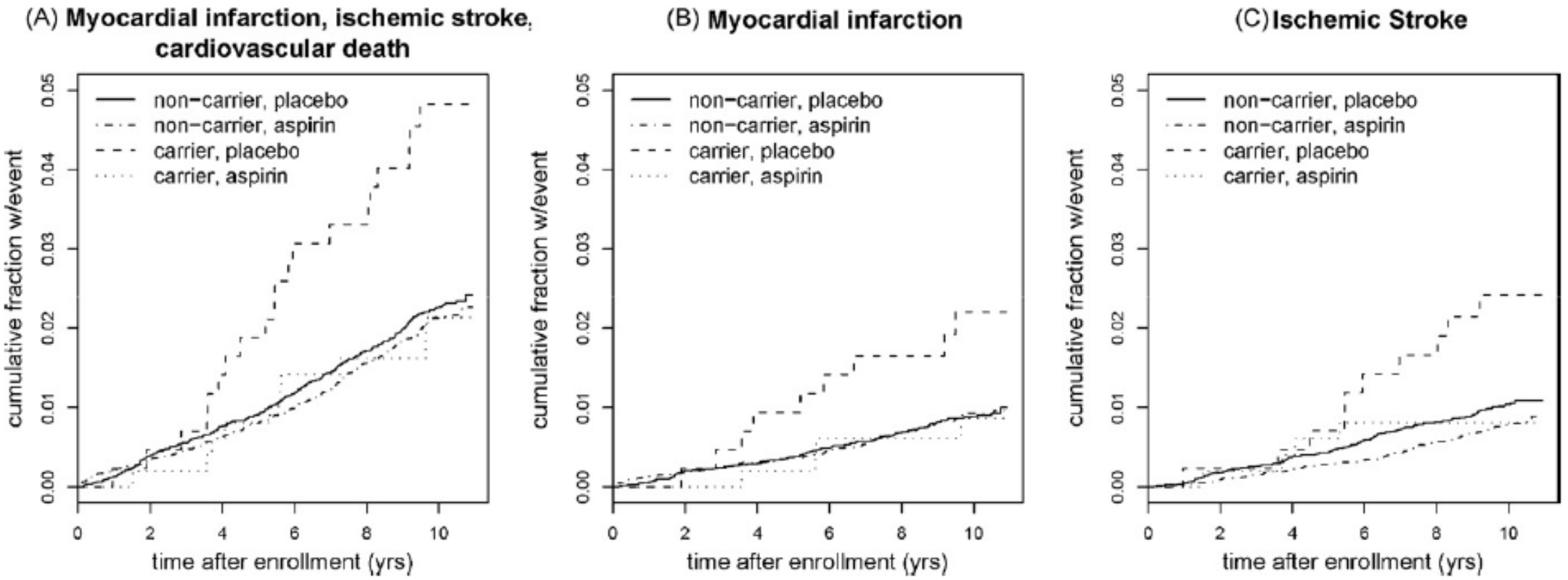
Followed for first major cardiovascular event – MI, ischemic stroke, cardiovascular death

Minor allele homozygotes baseline Lp(a) 153.9 mg/dL

- **MACE age-adjusted HR 0.44 (0.20 – 0.94) with ASA vs. placebo**

Chasman et as Atherosclerosis. 2009;203:371-6.

Aspirin and Lp(a)



Chasman et as Atherosclerosis. 2009;203:371-6.

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Emerging Therapeutic Options for Lp(a)

Sotirios Tsimikas, MD
Director of Vascular Medicine
Professor of Medicine
University of California San Diego

JACC FOCUS SEMINAR

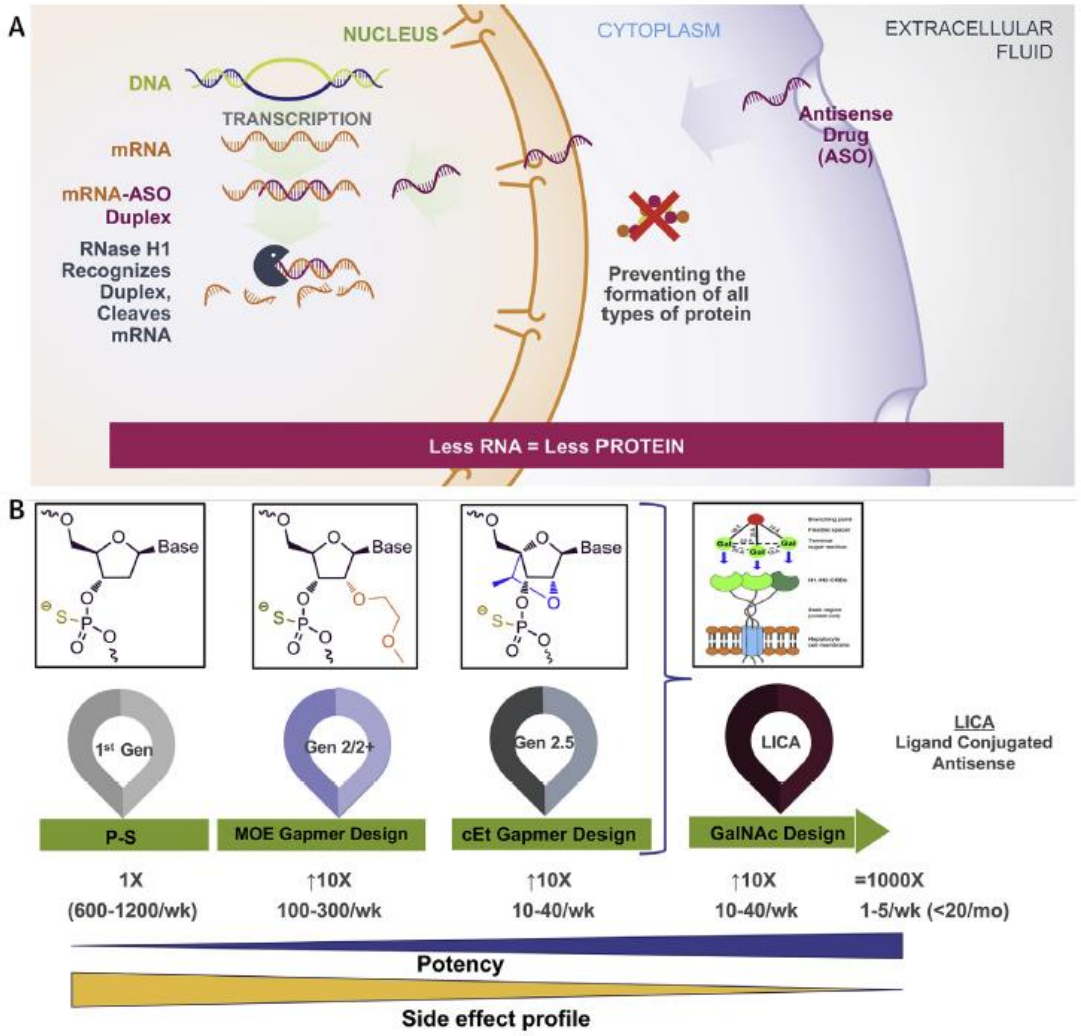
Emerging RNA Therapeutics to Lower Blood Levels of Lp(a)

JACC Focus Seminar 2/4

Sotirios Tsimikas, MD,[a] Patrick M. Moriarty, MD,[b] Erik S. Stroes, MD, PhD[c]

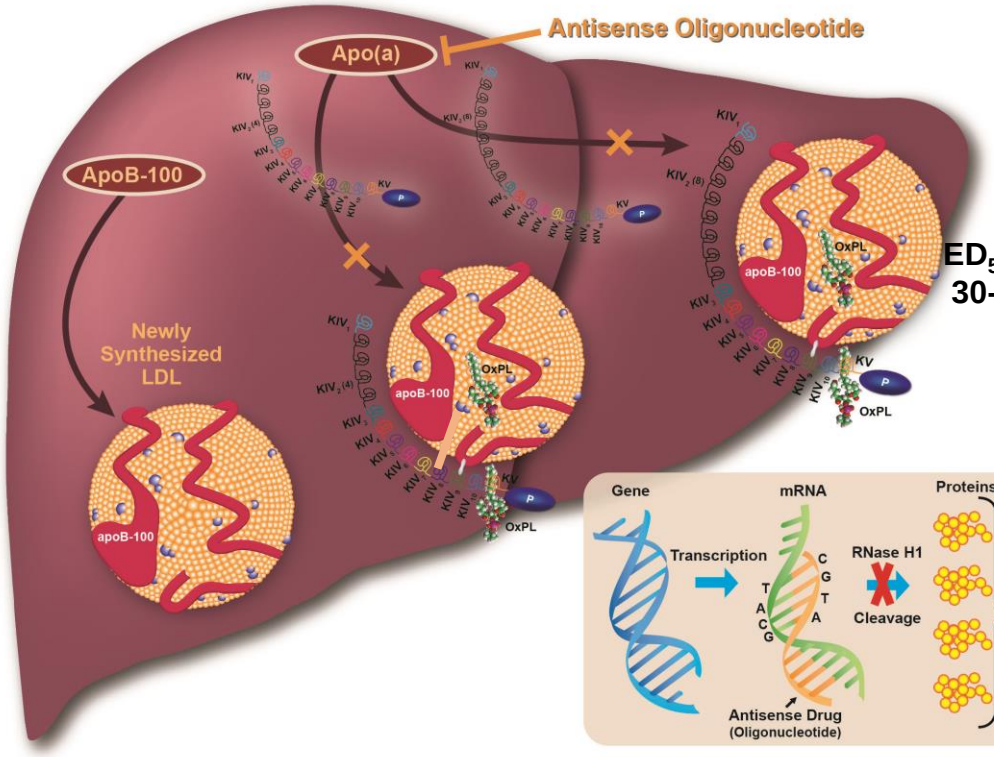
Tsimikas S, Moriarty PM, Stroes ES. J Am Coll Cardiol. 2021;77:1576-89.

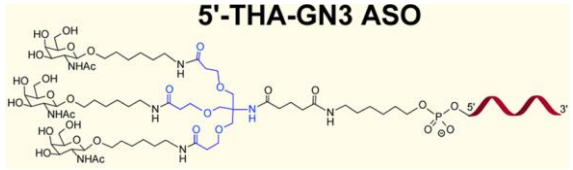
Mechanism of ASO Therapeutic Efficacy, Chemical Modifications, and Improvement in Potency



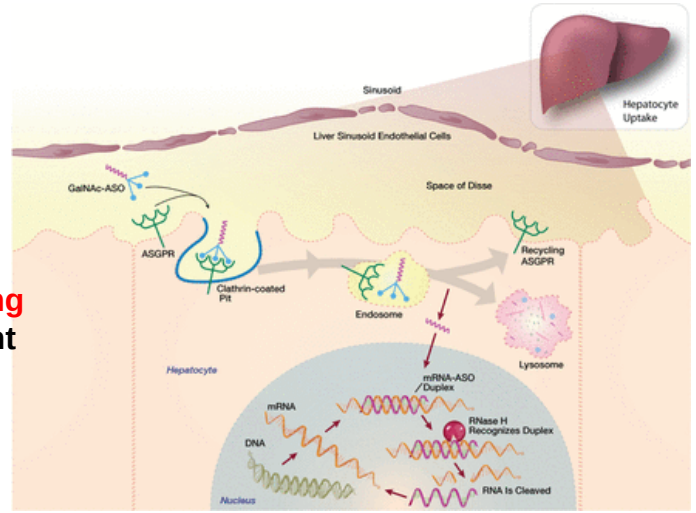
Tsimikas S, Moriarty PM, Stroes ES.
J Am Coll Cardiol. 2021;77:1576-89

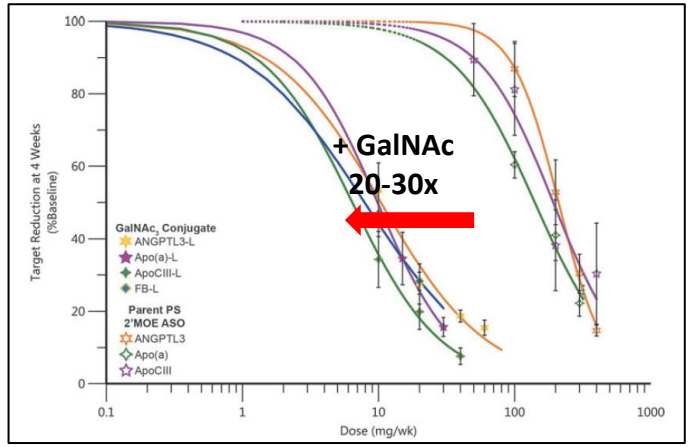
Antisense Oligonucleotides Targeting Lp(a)





Lp(a) ASO
ED_{50} 122 mg vs 4 mg
30-fold more potent

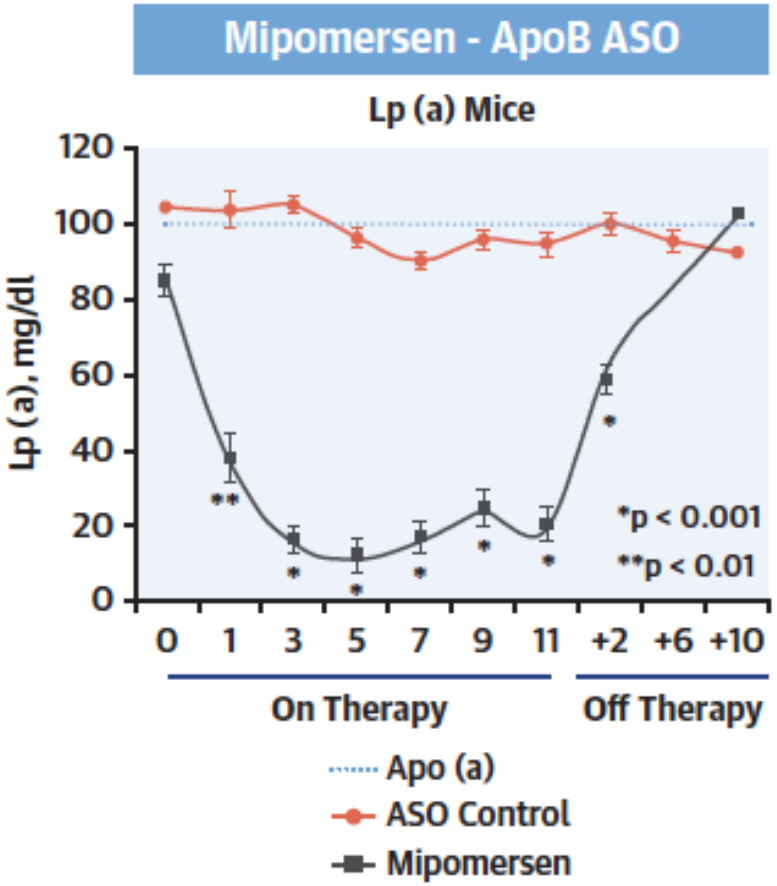




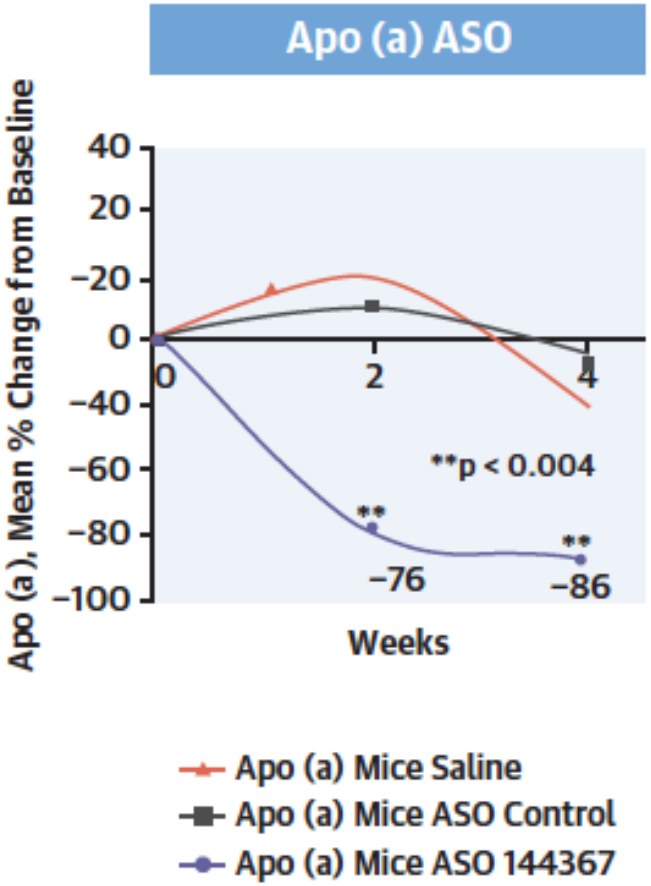
Prakash et al Nucl Acids Res 2014 42:8796-807
Crooke ST et al Nucl Acid Ther 2019;29:16-32

Tsimikas JACC 2017;69:692-711

First Pre-Clinical Studies Documenting ASOs Targeting Lp(a)



Merki E *et al. Circulation* 2008;118:743–53



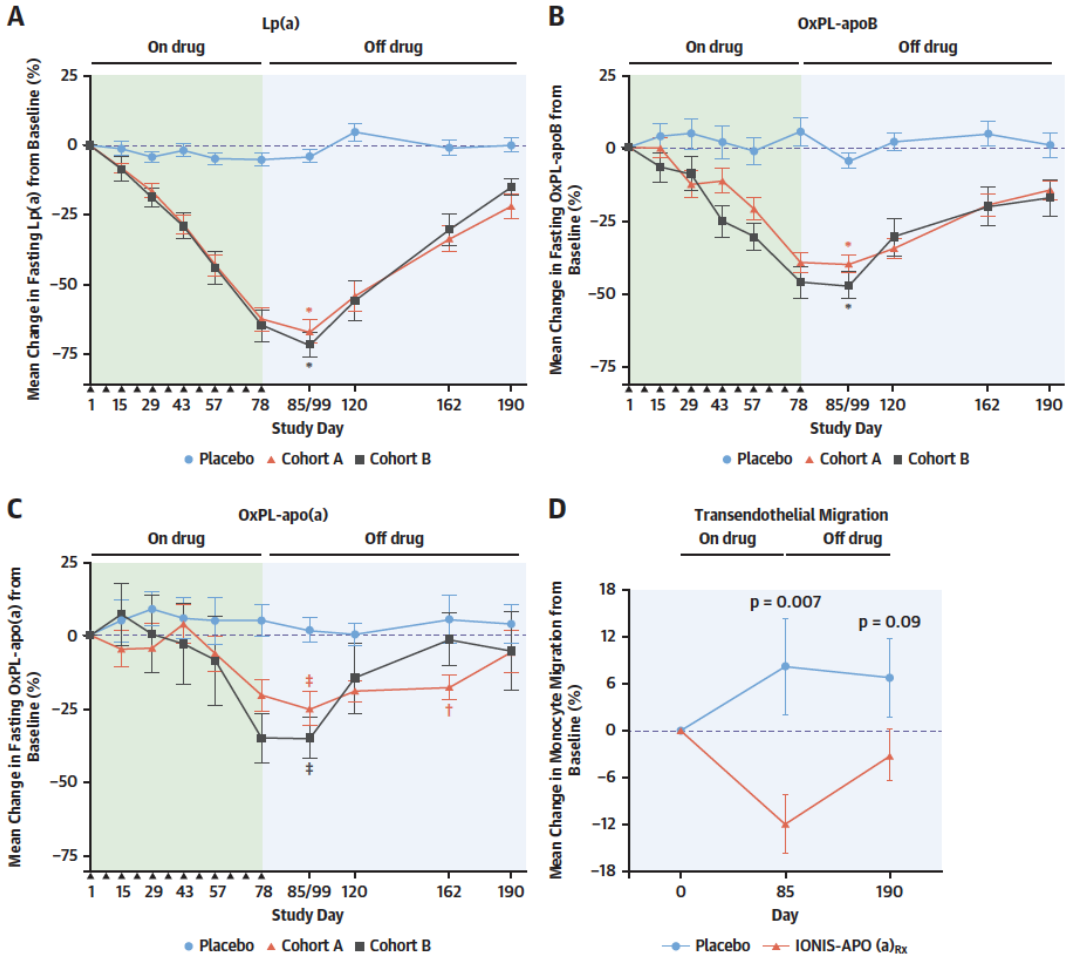
Merki E *et al. JACC* 2011;57:1611–2

Competed Clinical Trials in Lowering Lp(a) With Antisense Oligonucleotides

First Author (Ref. #)	Year Published	Drug	N	Dose/Dose Regimen	Mean Baseline Lp(a) (nmol/l)	Mean Lp(a) Reduction (%)	Absolute Lp(a) Reduction (nmol/l)
Tsimikas et al. (37)	2015	ISIS-APO(a)$_{Rx}$	16	Single doses of 50, 100, 200, and 400 mg	8–66	No significant change	N/A
			31	100, 200, and 300 mg/week, 6 doses over 4 weeks	82–152	40–78	34–95
Viney et al. (30)	2016	IONIS-APO(a)$_{Rx}$	50 (cohort A)	100–300 mg/week for 13 weeks	252–254	67	183
			11 (cohort B)	100–300 mg/week for 13 weeks	445–488	72	305
Viney et al. (30)	2016	Pelacarsen	28	Single doses of 10, 20, 40, 80, and 120 mg	111–219	26–85	59–107
			30	Multiple doses 10, 20, and 40 mg/week for 4 weeks	143–165	66–92	86–141
Tsimikas et al. (36)	2020	Pelacarsen	286	20, 40, or 60 mg every 4 weeks; 20 mg every 2 weeks; or 20 mg every week for 6–12 months	205–247	35–80	96–188

Tsimikas S, Moriarty PM, Stroes ES. J Am Coll Cardiol. 2021;77:1576-89

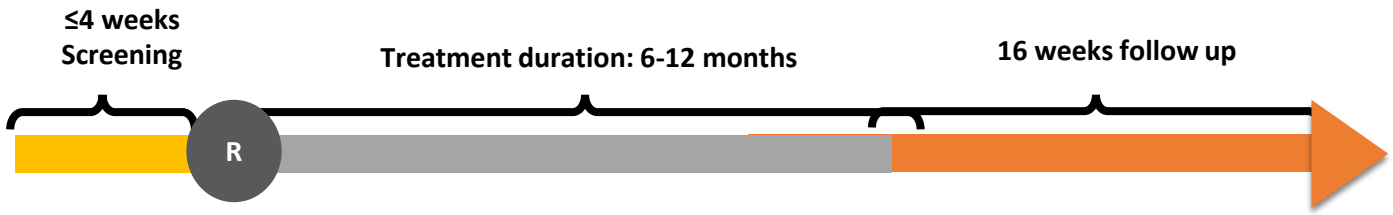
Effects of Pelacarsen on Lp(a), OxPL and Monocyte Transendothelial Migration



Viney et al. Lancet. 2016;388:2239-53.

Pelacarsen Phase 2 Trial

Study Design and Endpoints



Five cohorts*,
N per cohort=54,
randomized 5:1
(45 active, 9 placebo)

<u>*Cohorts (SC administration):</u>

20 mg or placebo Q4W
40 mg or placebo Q4W
60 mg or placebo Q4W
20 mg or placebo Q2W
20 mg or placebo QW

The primary endpoint was the mean percent change in Lp(a) from baseline to week 25–27 depending on dose regimen

Secondary endpoints included:

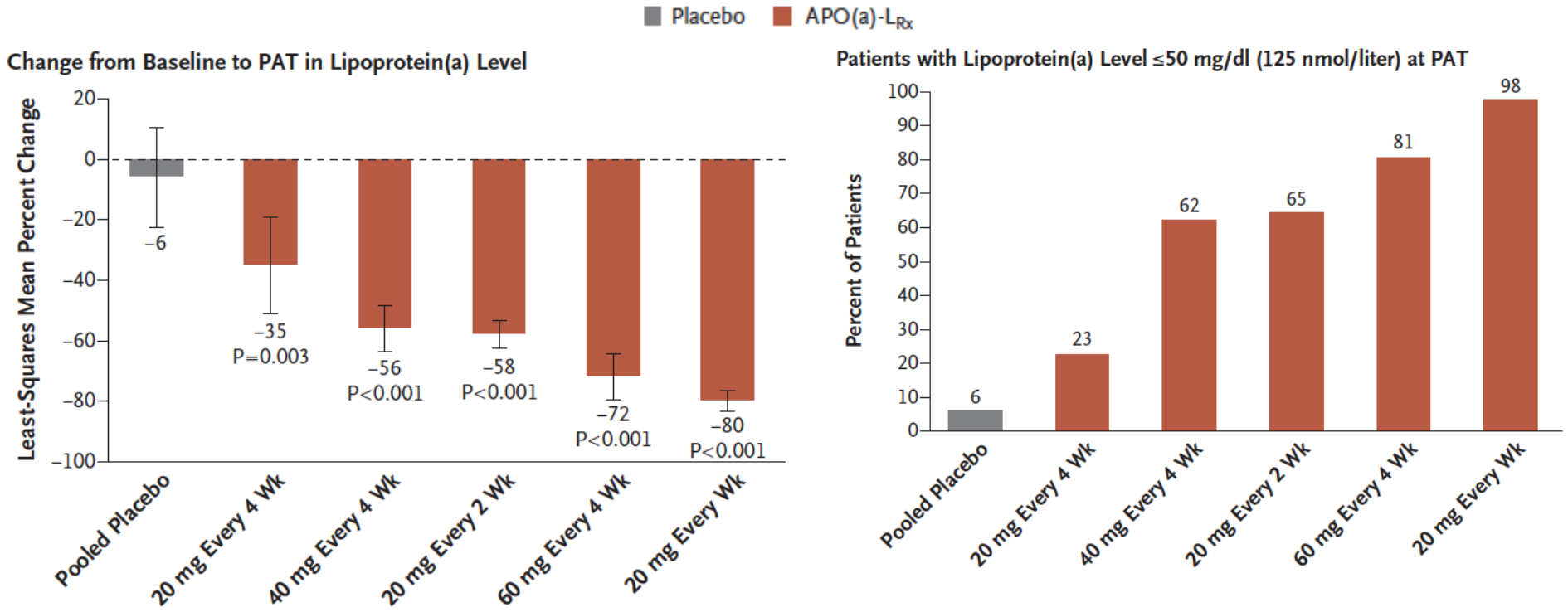
- **Mean percent change in OxPL-apoB, OxPL-apo(a), LDL-C, apoB and the percentage of patients reaching Lp(a) <50 mg/dL (<125 nmol/L)**

- QW = every week; Q2W = every 2 weeks; Q4W = every 4 weeks; R = randomization; SC = subcutaneous.

Tsimikas et al N Engl J Med 2020;382:244-55

Pelacarsen - mean 80% reduction in Lp(a)

98% of patients reached goals of <50 mg/dL (<125 nmol/L)
No significant differences in liver or renal function or platelet count



Tsimikas et al N Engl J Med 2020;382:244-55

Pelacarsen - Significant Reductions in Oxidized Phospholipids, LDL-C and ApoB

Table 2. Absolute Change from Baseline at 6 Months of Exposure.*

Measure	APO(a)-L_{Rx}					Pooled Placebo (N=47)
	20 mg Every 4 Wk (N=48)	40 mg Every 4 Wk (N=48)	20 mg Every 2 Wk (N=48)	60 mg Every 4 Wk (N=47)	20 mg Every Wk (N=48)	
Lipoprotein(a) — nmol/liter	−95.9±94.4	−116.9±71.7	−130.3±66.1	−149.5±67.4	−187.8±80.3	−15.2±34.6
Lipoprotein(a) — mg/dl	−38.4±7.7	−46.8±28.7	−52.1±26.4	−59.8±27.0	−75.1±32.1	−6.1±13.8
OxPL-apoB — nmol/liter	−8.0±10.3	−11.3±11.0	−12.2±7.9	−14.9±10.3	−20.1±8.5	3.7±8.1
OxPL-apo(a) — nmol/liter	−16.8±14.3	−24.5±20.1	−25.9±17.2	−33.3±16.8	−41.6±16.5	−12.3±14.7
LDL cholesterol — mg/dl	−5.6±27.4	−13.5±30.1	−13.2±19.8	−8.2±17.3	−16.4±14.8	−1.2±17.8
Apolipoprotein B — mg/dl	−2.2±17.4	−8.3±18.2	−6.3±11.6	−3.9±13.5	−10.9±10.9	0.6±12.0
Total cholesterol — mg/dl	−3.9±32.1	−11.6±32.1	−11.6±24.4	−3.9±23.2	−11.6±20.9	−3.9±21.3
HDL cholesterol — mg/dl	0.0±6.2	0.0±9.7	3.7±8.9	3.7±11.6	3.7±10.1	0.0±6.6
Triglycerides — mg/dl	−8.9±32.8	−8.9±31.0	0.0±52.3	0.0±50.5	−8.9±41.6	0.0±51.4
hsCRP — mg/liter	−0.9±4.24	−0.7±4.24	−0.3±2.84	−0.5±2.22	−0.1±6.30	−0.8±5.13

Tsimikas et al N Engl J Med 2020;382:244-55

Estimated Lp(a)-Lowering Effect Size for Reduction in Coronary Heart Disease Outcomes Relative to 38.67-mg/dL LDL-C Reduction

First Author (Ref. #)	Year Published	Study Design	N	Population Type	Estimated Lp(a) Reduction
Burgess et al. (40)	2018	Mendelian randomization	48,333	Primary prevention	101.5 mg/dl
Parish et al. (43)	2018	Clinical trial	3,978	Secondary prevention	80 nmol/l (~32 mg/dl)
Lamina et al. (41)	2019	Mendelian randomization	62,114	Primary prevention	65.7 mg/dl
Madsen et al. (42)	2020	Mendelian randomization	58,527	Primary prevention	50 mg/dl (105 nmol/l)
Szarek et al. (18)	2020	Clinical trial	18,924	Secondary prevention	40 mg/dl

Tsimikas S, Moriarty PM, Stroes ES. J Am Coll Cardiol. 2021;77:1576-89

Lp(a)-HORIZON CVOT - NCT04023552

Study population: **7680 patients with established CVD (prior MI, stroke, PAD) and Lp(a) ≥70 mg/dL with optimal therapy for cholesterol lowering and other CV risk factors**

Objectives: **Demonstrate superiority of TQJ230 80 mg sc monthly vs. placebo in reducing the risk of extended MACE (MI, stroke, CV death or urgent coronary revascularization) in the overall study population and in a subpopulation of patients with Lp(a) ≥90 mg/dL**

Co-Primary Endpoint:

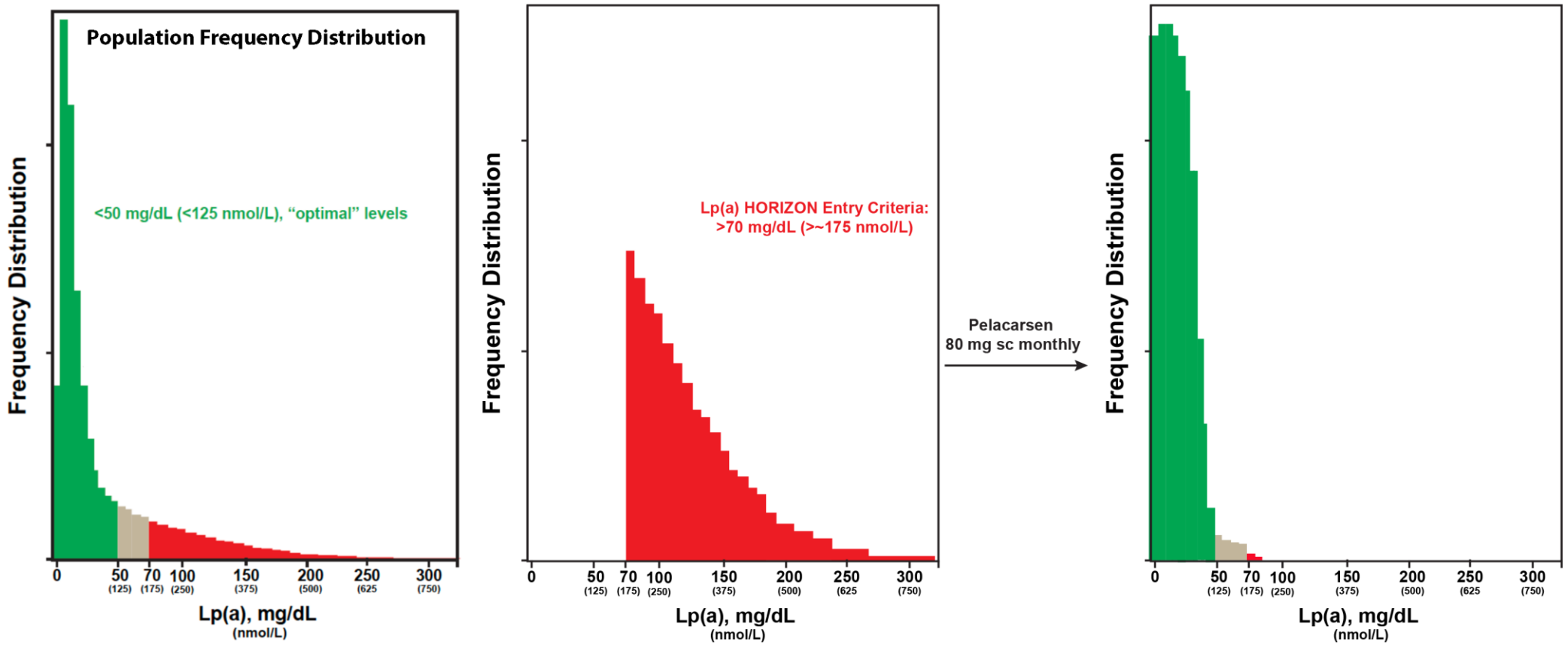
1- Time to first occurrence of MACE (cardiovascular death, non-fatal MI, non-fatal stroke and urgent coronary re-vascularization requiring hospitalization) in patients with elevated Lp(a) ≥ 70 mg/dL at 4 years

2- Time to first occurrence of MACE (cardiovascular death, non-fatal MI, non-fatal stroke and urgent coronary re-vascularization requiring hospitalization) in patients with elevated Lp(a) ≥ 90 mg/dL at 4 years

Median F/U: **~4.2 years, minimal 2.5 years, 993 events**

Study will be positive if primary endpoint is met in either overall or sub-population

Lp(a) HORIZON- Anticipated Frequency Distribution of Baseline and On-Treatment Lp(a) Levels Following Pelacarsen



Tsimikas S, Moriarty PM, Stroes ES. J Am Coll Cardiol. 2021;77:1576-89

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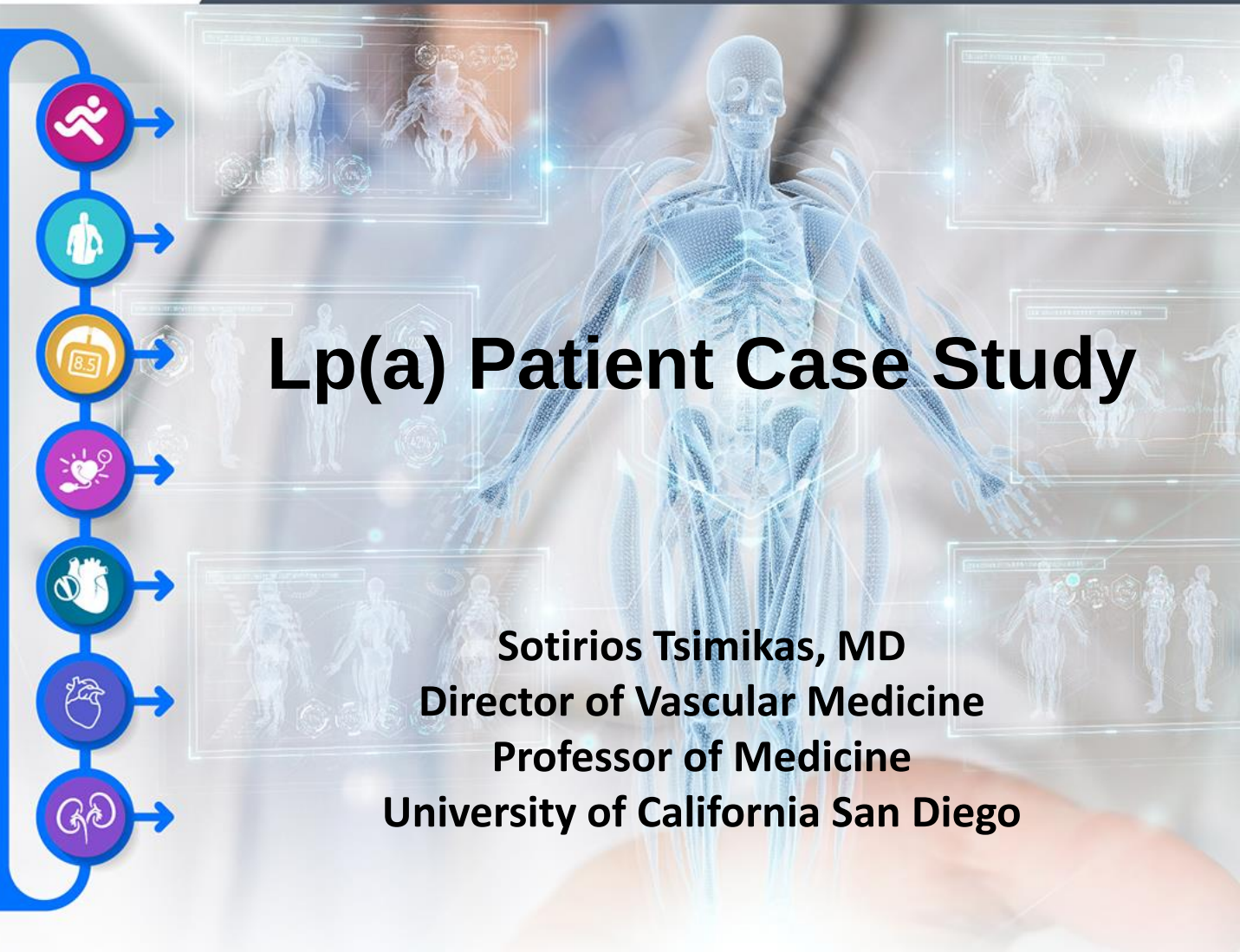


Lp(a) Patient Case Study

Sotirios Tsimikas, MD
Director of Vascular Medicine
Professor of Medicine
University of California San Diego

Lp(a)
Case Studies

Case #1

UCSD is a Center of Excellence in Research and Patient Care in Lp(a)

Dedicated "Lp(a) Clinic" since 2014

Atherosclerosis 300 (2020) 1–9

Contents lists available at ScienceDirect

Atherosclerosis

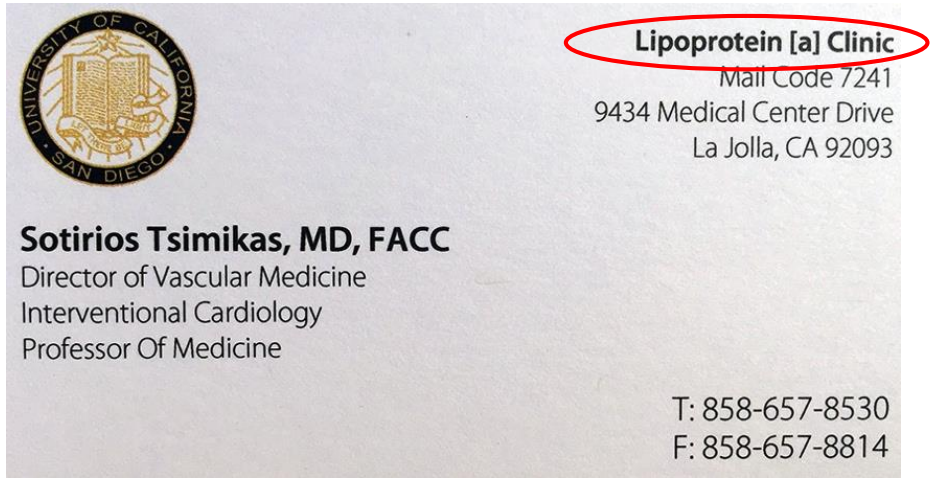
journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

The dedicated "Lp(a) clinic": A concept whose time has arrived?

Sotirios Tsimikas[a,b,**], Erik S.G. Stroes[a,b]

[a] Vascular Medicine Program, Sulpizio Cardiovascular Center, Division of Cardiology, Department of Medicine, University of California San Diego, La Jolla, CA, USA
[b] Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands



Physician members of the UCSD Lp(a) Clinic:

Michael Wilkinson, MD
Calvin Yeang, MD
Joseph Witztum, MD
Sotirios Tsimikas, MD

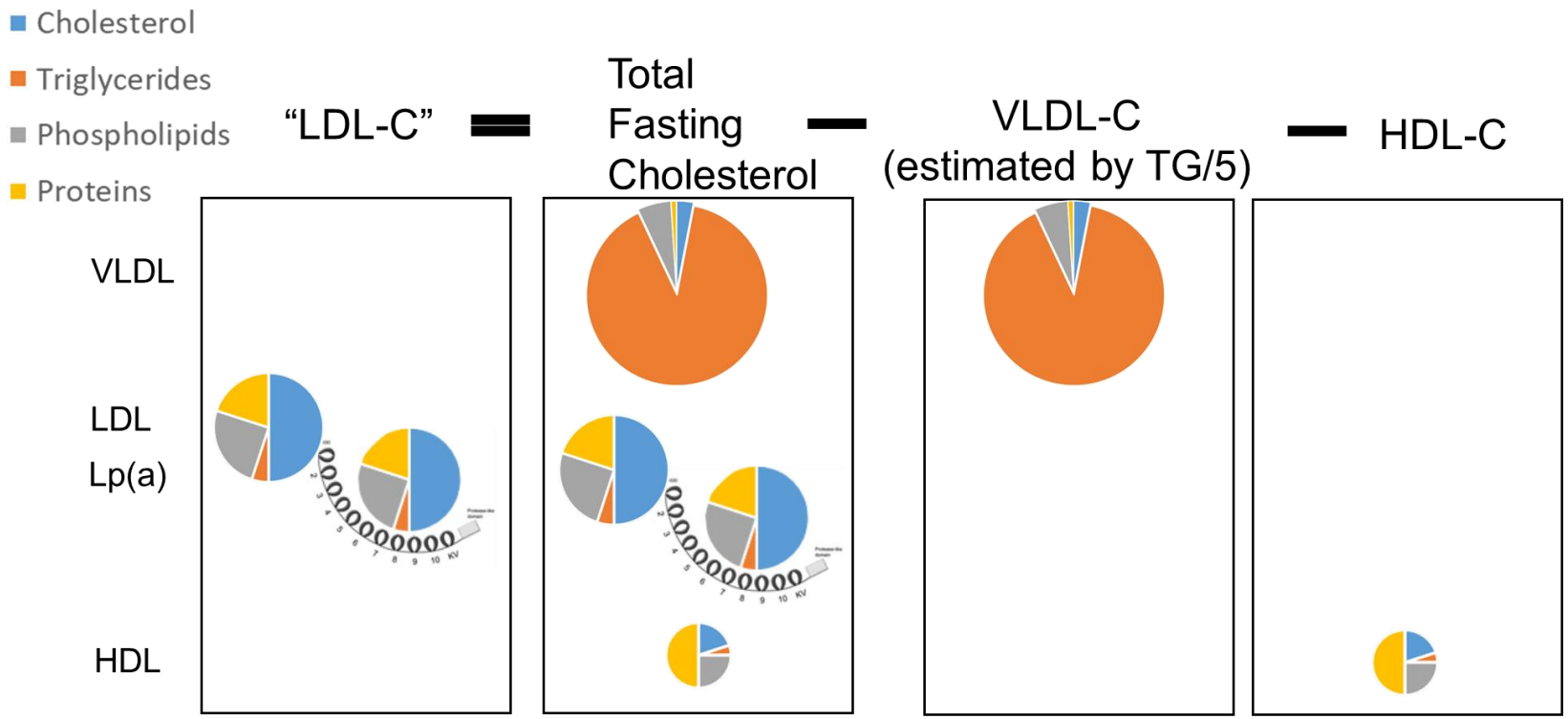
'LDL-C' = LDL-C + Lp(a)-C: implications of achieved ultra-low LDL-C levels in the proprotein convertase subtilisin/kexin type 9 era of potent LDL-C lowering

Calvin Yeang, Joseph L. Witztum, and Sotirios Tsimikas

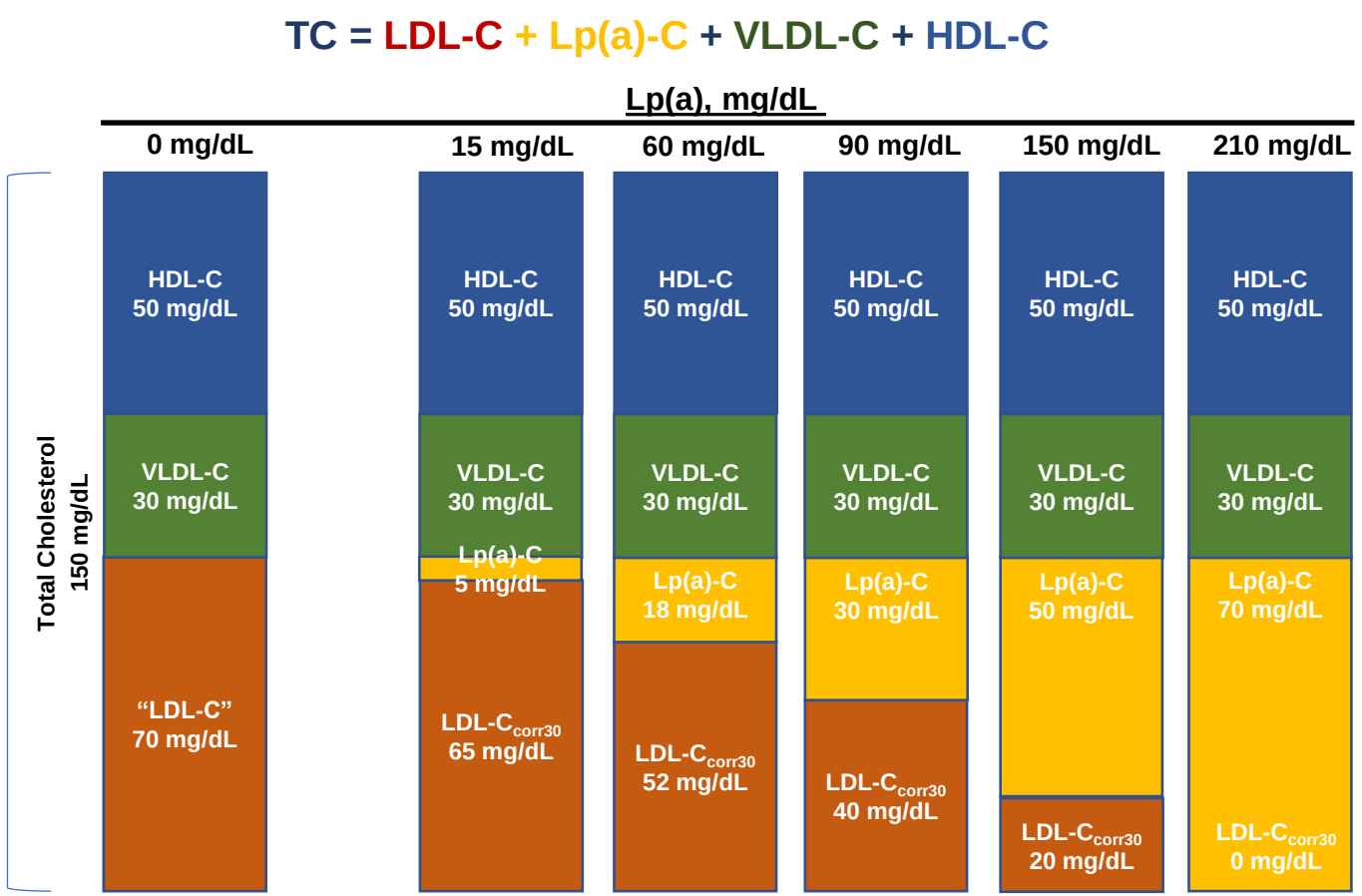
Yeang/Witztum/Tsimikas et al Curr Opin Lipidol 2015;26:169-78

Existing clinical “LDL-C” assays cannot distinguish LDL from Lp(a)

Friedewald calculation estimates “LDL-C”, but it includes Lp(a)-C



Effect of Lp(a) mass on “LDL-C”

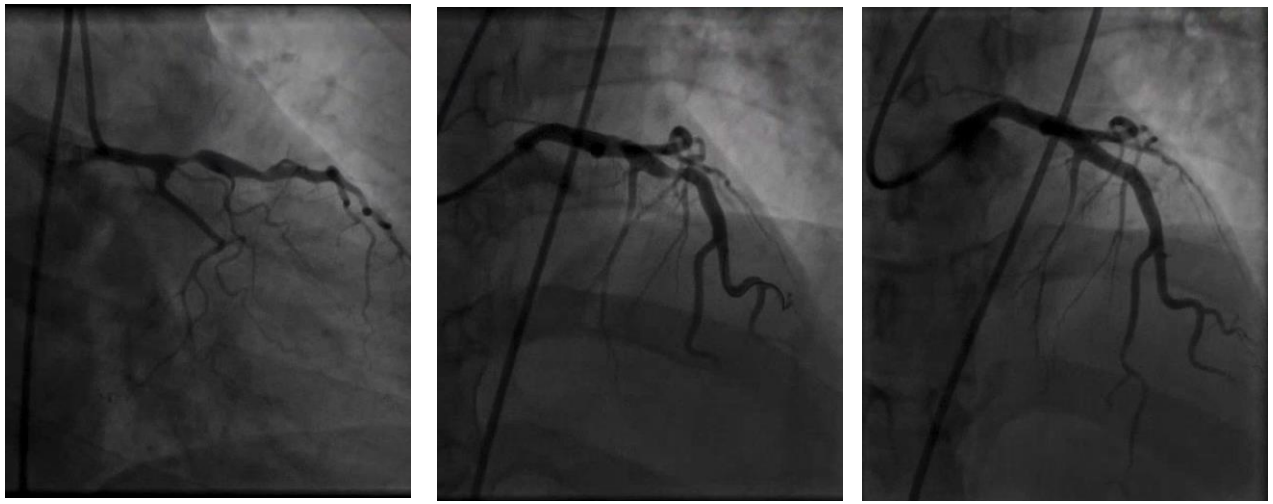


Tsimikas/Stroes: The dedicated ”Lp(a) clinic": A concept whose time has arrived? Athero 2020;300:1-9

UCSD Lp(a) Clinic Case

Lp(a) as a Cause of “Statin Resistance”

- **49 yo female with mild obesity, father had MI at 63, no other CVD risk factors**
- **Presented with ACS, small troponin increase**
- **Angiogram with hazy, 90% stenosis of LAD, no other lesions**
- **Received 4x33 Xience stent, placed on ATV 80, documented to be filling prescriptions in chart**



UCSD Lp(a) Clinic Case

- **Lipid panel on presentation:**
  - **TC-163, LDL-C-85, HDL-51, TG-134**
  - **What is etiology of CAD?**
- **Placed on 80 mg atorvastatin, lipid panel 6 months later**
  - **TC-173, LDL-C-82, HDL-69, TG-110**
  - **Is this statin resistance?**

UCSD Lp(a) Clinic Case

- Lp(a) - 225 mg/dL
  - Assume Lp(a) mass is 30% chol, Lp(a)-C is 75 mg/dL
  - True “LDL-C = LDL-C – Lp(a)-C”
  - 82 - 75 mg/dL = 7 mg/dL
  - ATV 80 reduced true LDL-C from 10 to 7 mg/dL, -30% reduction

- Placed on niacin, dose slowly increased to 1500 mg/dL
- Lipid panel 5 months later:
  - TC= 141, LDL-C= 46, HDL-C= 76, TG= 94, Lp(a)= 170 mg/dL
- Lipid panel 1 yr later:
  - TC= 110, LDL-C= 34, HDL-C= 56, TG= 98, Lp(a)= 55 mg/dL

UCSD Lp(a) Clinic – Clinical Pearls

- **Elevated Lp(a) is often present in young patients with MI, particularly when family history is present**
- **Lack of responsiveness to statin therapy may be due to elevated Lp(a)**
- **If you don't get the expected decline in LDL-C and patient is compliant with medications, check an Lp(a) level**

Lp(a)- Conclusions and Take Home Messages

1) **Clinical expression is manifested in all arterial sites and aortic valve**
2) **Lp(a) in a highly prevalent, independent, genetic risk factor for CVD**
3) **Risk of Lp(a) is nearly linear to plasma levels**
4) **Measuring Lp(a) is now recommended in 7 guidelines**
5) **Patients with elevated Lp(a) have much lower true LDL-C than appreciated**
6) **Statins often increase Lp(a)**
7) **PCSK9 inhibitors are weakly effective in patients with Lp(a) >50 mg/dL but may be associated with reduction in MACE if Lp(a) is elevated**
8) **A highly effective therapy has finished phase 2**
9) **The "Lp(a) Hypothesis" is being tested in the Phase 3 Lp(a) HORIZON CVOT.**

Lp(a)- Multiple Choice Questions

According to the 2018 ACC/AHA Cholesterol guidelines, which of the following is a risk enhancer?

A- Lp(a) >30 mg/dL
B- apoB >100 mg/dL
C- triglycerides > 2 mmol/L
D- ankle-brachial index < 1

Lp(a)- Multiple Choice Questions

The data for Lp(a) as a CVD risk factor is stronger in:

A- Secondary prevention
B- Primary prevention
C- Genetic analyses
D- Acute coronary syndromes

Lp(a)- Multiple Choice Questions

For which clinical phenotype does Lp(a) have the strongest association?

A- Coronary artery disease
B- Acute myocardial infarction
C- Stroke/TIA
D- Aortic stenosis

Lp(a)- Multiple Choice Questions

What is the best characterization for the pathophysiological role of Lp(a) in CVD?:

A- Atherosclerosis via the apolipoprotein(a) component
B- Cholesterol content of the apolipoprotein(a) component
C- Interplay of atherosclerosis, inflammation and antifibrinolytic effects
D- Apolipoprotein(a) component binding to the endothelium

Lp(a)- Multiple Choice Questions

Which biomarker/risk factor would be best measured in a 42 yo thin male of South Asian ancestry with LDL-C 122/TG 148 and whose father died suddenly at age 48 in to best predict outcome?:

A- hsCRP
B- Lp(a)
C- 9P21 gene snp
D- red cell fatty acid content

Lp(a)- Multiple Choice Questions

Word association- which of these pairs go best together?:

A- apolipoprotein(a)-fibrinogen
B- Lp(a)– directly pro-thrombotic
C- small dense LDL – oxidized phospholipids
D- Antisense oligonucleotide - pelacarsen