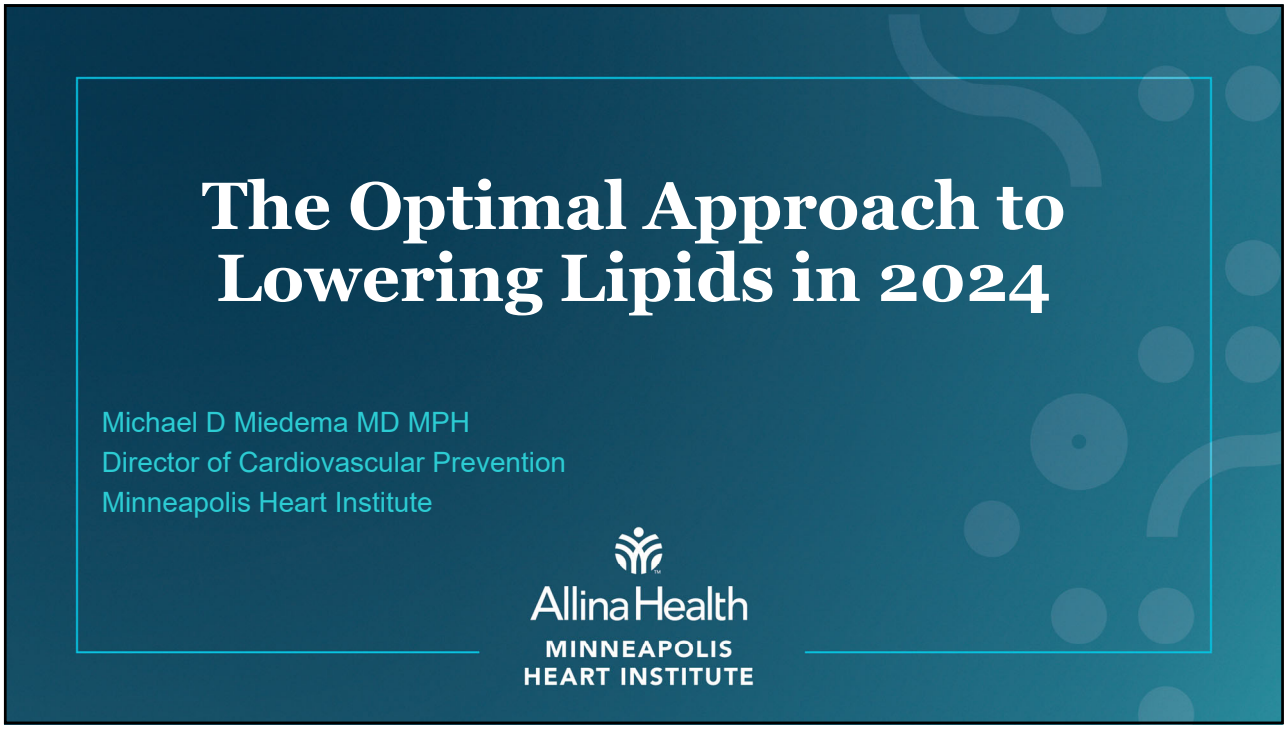

Minneapolis Heart Institute Foundation
GRAND ROUNDS

1


The Optimal Approach to Lowering Lipids in 2024
Michael D Miedema MD MPH
Director of Cardiovascular Prevention
Minneapolis Heart Institute
Allina Health
MINNEAPOLIS HEART INSTITUTE

2

Disclosures

- None

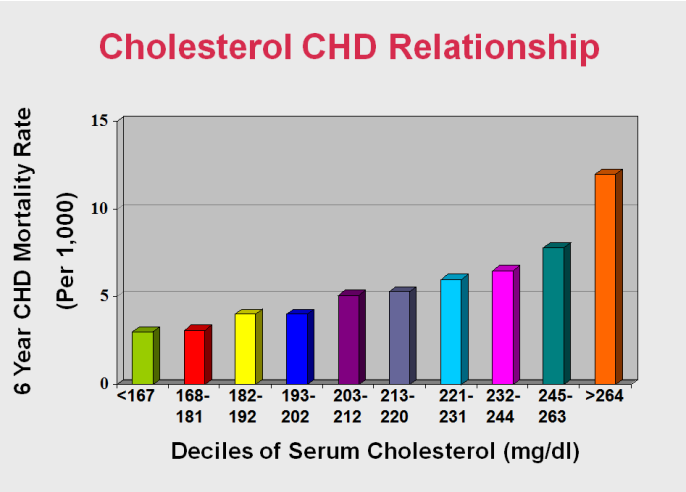
3

Objectives

- Current Approach to lipid-lowering therapy
- Future Directions

4

The Relationship Between Cholesterol and CHD is Linear

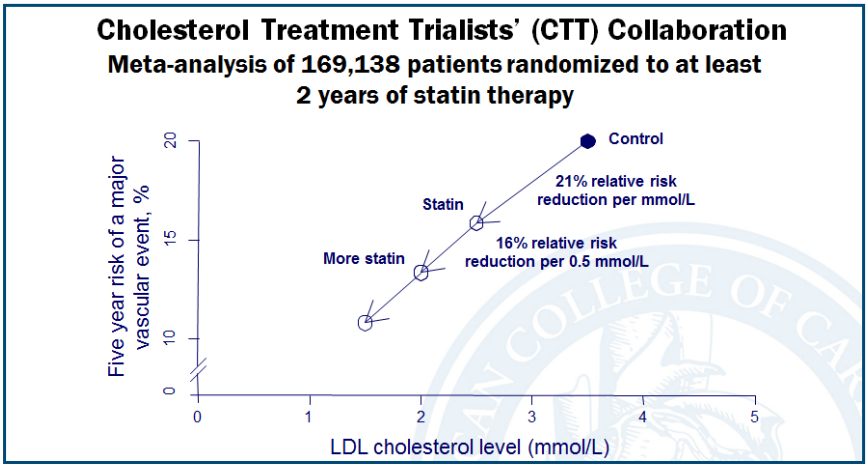


MrFIT JAMA 1986

AllinaHealth MINNEAPOLIS HEART INSTITUTE

5

Statin Good - More Statin Better



AllinaHealth MINNEAPOLIS HEART INSTITUTE

6

Statin Safety

Effect of statin therapy on muscle symptoms: an individual participant data meta-analysis of large-scale, randomised, double-blind trials

*Cholesterol Treatment Trialists' Collaboration**

7

Statin vs Placebo

(A) Statin vs placebo	(n=62 028)	(n=61 912)			
Myalgia	7446 (12·0%)	7269 (11·7%)	120·1	3657·4	1·03 (0·99–1·08)
Limb pain	1850 (3·0%)	1836 (3·0%)	3·6	921·3	1·00 (0·92–1·09)
Other musculoskeletal pain	8245 (13·3%)	8037 (13·0%)	131·3	4066·1	1·03 (0·99–1·08)
Muscle cramp or spasm	1697 (2·7%)	1553 (2·5%)	71·2	812·4	1·09 (1·00–1·19)
Any muscle pain	**16 656 (26·9%)**	**16 281 (26·3%)**	**274·8**	**8206·8**	**1·03 (1·01–1·06)**
Muscle fatigue or weakness	445 (0·7%)	406 (0·7%)	19·4	212·7	1·10 (0·92–1·31)
Any muscle pain or weakness	**16 835 (27·1%)**	**16 446 (26·6%)**	**283·1**	**8292·7**	**1·03 (1·01–1·06)**

8

More verses Less Intensive

(B) More vs less intensive statin	(n=15390)	(n=15334)			
Myalgia	3485 (22·6%)	3380 (22·0%)	70·2	1712·7	1·04 (0·98–1·11)
Limb pain	619 (4·0%)	603 (3·9%)	7·3	305·5	1·02 (0·88–1·19)
Other musculoskeletal pain	1721 (11·2%)	1628 (10·6%)	47·8	836·9	1·06 (0·97–1·16)
Muscle cramp or spasm	515 (3·3%)	495 (3·2%)	10·3	252·5	1·04 (0·89–1·22)
Any muscle pain	**5490 (35·7%)**	**5274 (34·4%)**	**132·0**	**2686·6**	**1·05 (1·01–1·09)**
Muscle fatigue or weakness	158 (1·0%)	148 (1·0%)	4·9	76·5	1·07 (0·79–1·43)
Any muscle pain or weakness	**5558 (36·1%)**	**5342 (34·8%)**	**132·8**	**2720·5**	**1·05 (1·01–1·09)**

99% CI 95% CI

0·8 1·0 1·2 1·4 1·6

Favours statin or more intense statin | Favours placebo or less intense statin

AllinaHealth MINNEAPOLIS HEART INSTITUTE

Statin therapy and muscle symptoms - Lancet 2022

9

Early versus Late Reactions

Women>Men?

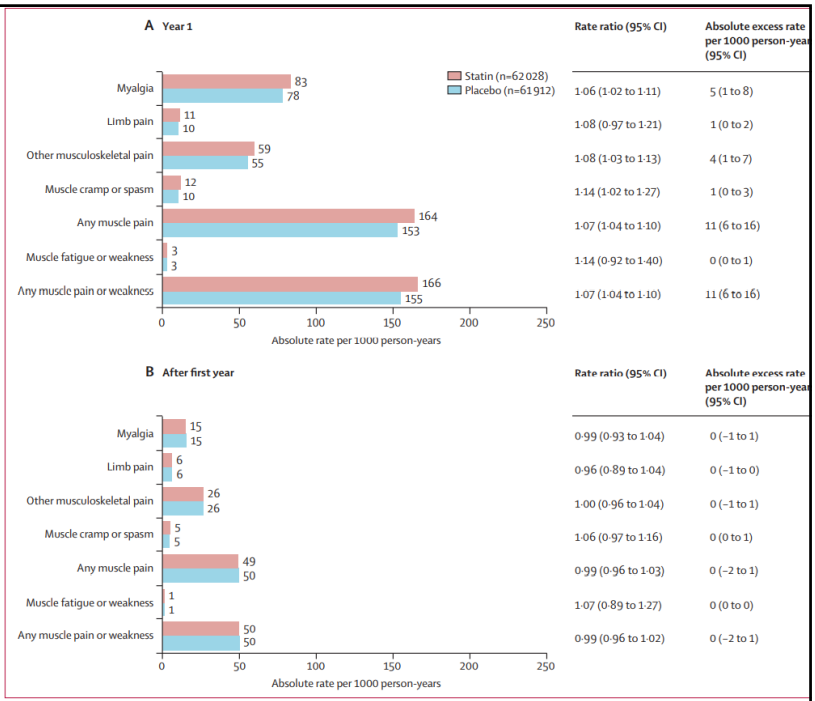


Figure 3: Rate ratio and absolute rate difference for muscle adverse events by duration of treatment, in trials of any statin regimen versus placebo

Statin therapy and muscle symptoms - Lancet 2022

AllinaHealth MINNEAPOLIS HEART INSTITUTE

10

The SAMSON Trial

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 78, NO. 12, 2021

Side Effect Patterns in a Crossover Trial of Statin, Placebo, and No Treatment

James P. Howard, PhD,[a,*] Frances A. Wood, MPhil,[a,*] Judith A. Finegold, PhD,[a] Alexandra N. Nowbar, MBBS,[a] David M. Thompson, PhD,[a] Ahran D. Arnold, MBBS,[a] Christopher A. Rajkumar, MBBS,[a] Susan Connolly, PhD,[a] Jaimini Cegla, PhD,[b] Chris Stride, PhD,[c] Peter Sever, PhD,[a] Christine Norton, PhD,[d] Simon A.M. Thom, MD,[a] Matthew J. Shun-Shin, PhD,[a] Darrel P. Francis, MA[a]

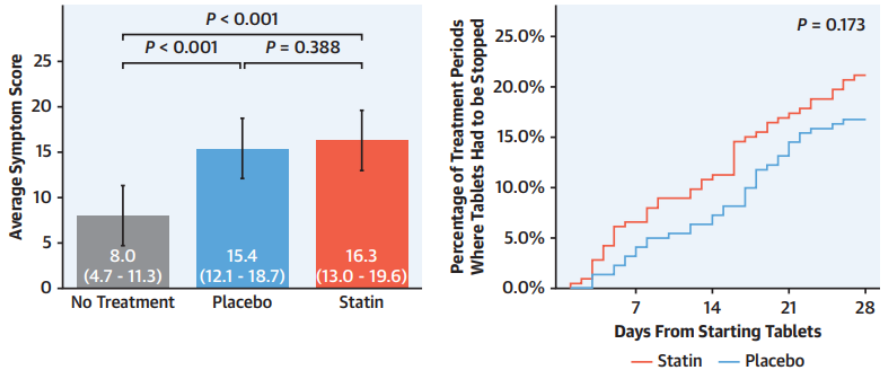
AllinaHealth MINNEAPOLIS HEART INSTITUTE

SAMSON Trial, JACC, 2021

11

The Power of the Nocebo Effect

CENTRAL ILLUSTRATION Symptom Scores and Cumulative Early Tablet Stopping Rates by Treatment



Howard, J.P. et al. J Am Coll Cardiol. 2021;78(12):1210-1222.

(Left) The mean symptom scores across the 3 treatment types (statin, placebo, and no treatment). **Whiskers** indicate the associated 95% CIs. **(Right)** The cumulative rate of stopping tablets for patients starting a statin **(red)** or placebo **(blue)** after a no-tablet month. *P* value derived from a mixed-effects logistic regression model.

AllinaHealth MINNEAPOLIS HEART INSTITUTE

SAMSON Trial, JACC, 2021

12

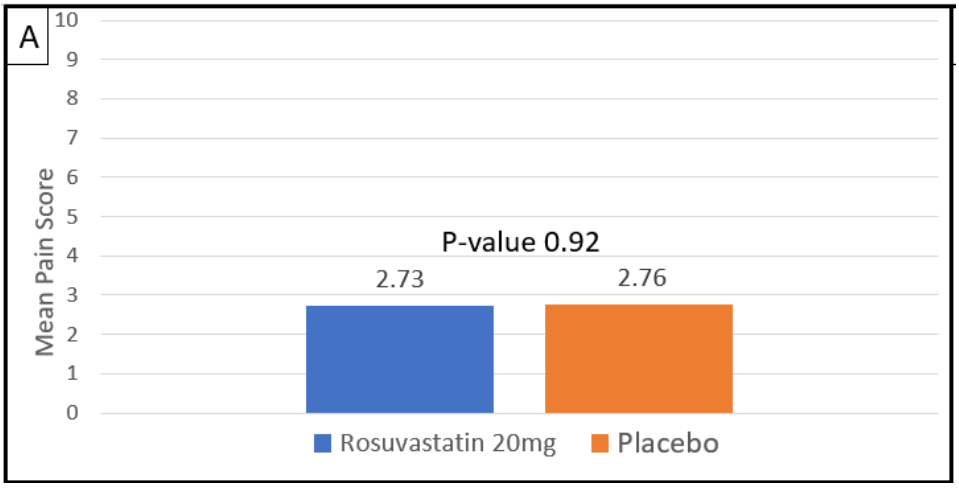
DEtermining Statin Intolerance For Rosuvastatin

- Adults with intolerance to 2 prior statins
  - Primary or Secondary Prevention
  - Trial can occur on other lipids lowering therapy
- Double blinded randomized “N of 1” Trial
- 6 month study
  - 3 4-week courses of placebo
  - 2 4-week courses of 20mg of rosuvastatin
  - 1 week break in between each course
- 3-month unblinded trial of rosuvastatin for those with no evidence of statin intolerance

Allina Health MINNEAPOLIS HEART INSTITUTE

13

Mean Pain Score

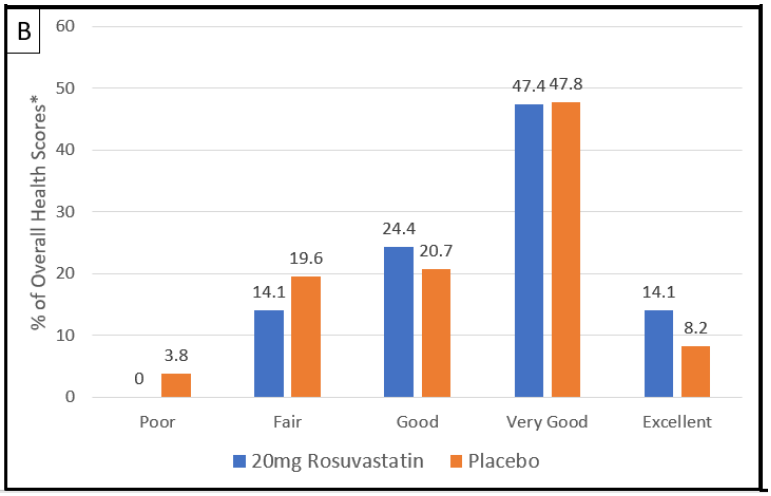


- 129 weeks on rosuvastatin vs 176 weeks of placebo

Allina Health MINNEAPOLIS HEART INSTITUTE

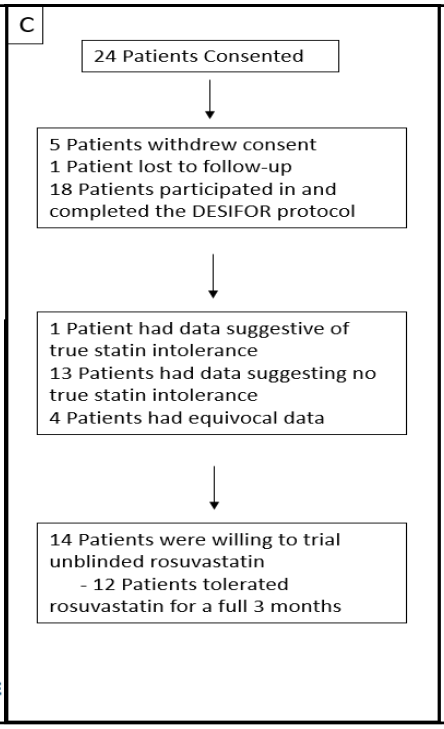
14

Overall Health Scores



AllinaHealth MINNEAPOLIS HEART INSTITUTE

15



AllinaHealth MINNEAPOLIS HEART INSTITUTE

16

The DESIFOR Trial

JACC: Advances

Letters

RESEARCH LETTER

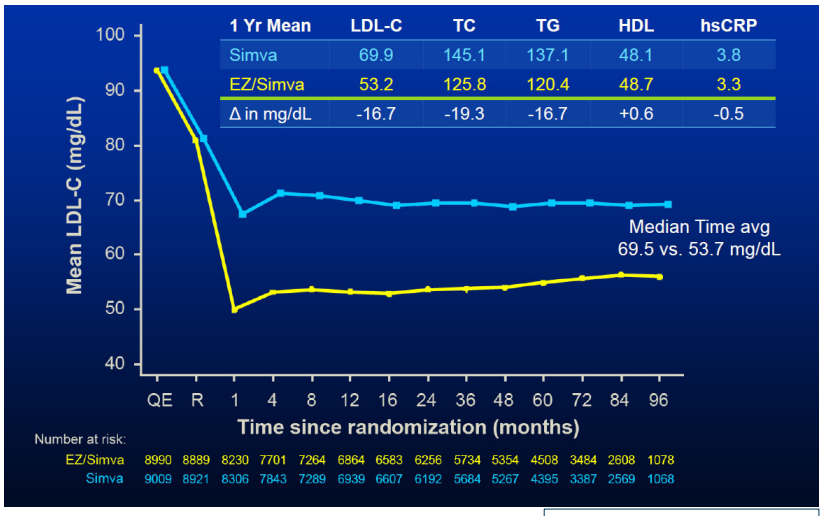
A Double-Blinded Randomized N-of-1 Trial to Facilitate Tolerance of Unblinded Rosuvastatin

The DESIFOR Pilot Trial

Allina Health MINNEAPOLIS HEART INSTITUTE

17

IMPROVE-IT Trial – Ezetimibe in addition to statin therapy

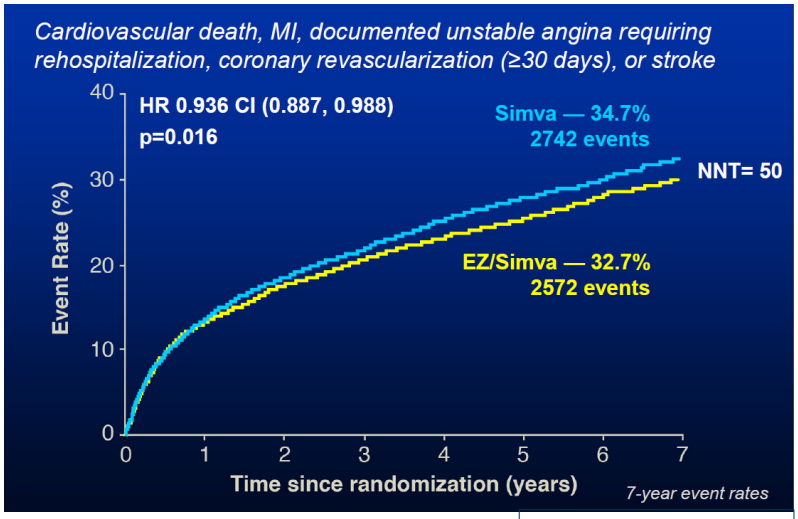


IMPROVE-IT, NEJM, 2014

Allina Health MINNEAPOLIS HEART INSTITUTE

18

IMPROVE-IT Trial – Ezetimibe in addition to statin therapy



IMPROVE-IT, NEJM, 2014

AllinaHealth MINNEAPOLIS HEART INSTITUTE

19

ORIGINAL INVESTIGATIONS

Atherothrombotic Risk Stratification and Ezetimibe for Secondary Prevention

Erin A. Bohula, MD, DPHIL,[a] David A. Morrow, MD, MPH,[a] Robert P. Giugliano, MD, SM,[a] Michael A. Blazing, MD,[b] Ping He, MS,[a] Jeong-Gun Park, PHD,[a] Sabina A. Murphy, MPH,[a] Jennifer A. White, MS,[b] Y. Antero Kesaniemi, MD, PHD,[c] Terje R. Pedersen, MD, PHD,[d] Adrian J. Brady, MD,[e] Yale Mitchel, MD,[f] Christopher P. Cannon, MD,[a] Eugene Braunwald, MD[a]

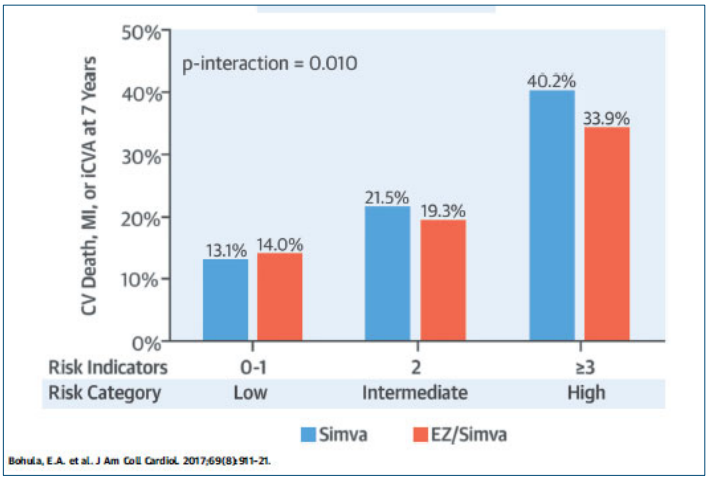
AllinaHealth MINNEAPOLIS HEART INSTITUTE

Ezetimibe-Risk Stratification, JACC, 2017

20

The Importance of Risk Stratification

TRS 2°P Risk Indicators	Points
CHF	1
HTN	1
Age ≥75	1
DM	1
Prior Stroke	1
Prior CABG	1
PAD	1
eGFR <60	1
Smoking	1
Maximum Possible	9



AllinaHealth MINNEAPOLIS HEART INSTITUTE

Ezetimibe-Risk Stratification, JACC, 2017

21

PCSK9 Inhibitors

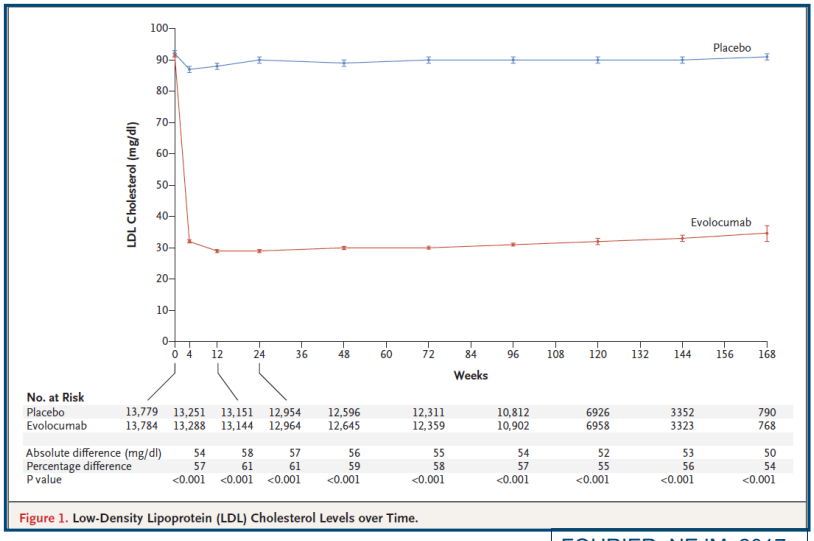


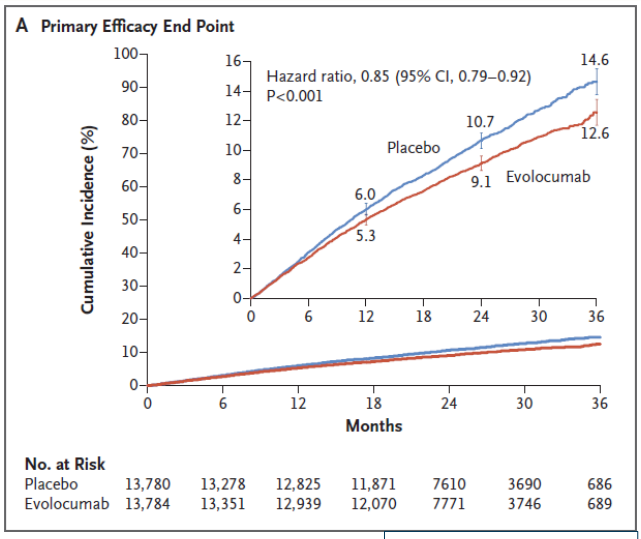
Figure 1. Low-Density Lipoprotein (LDL) Cholesterol Levels over Time.

FOURIER, NEJM, 2017

AllinaHealth MINNEAPOLIS HEART INSTITUTE

22

PCSK9 Inhibitors



FOURIER, NEJM, 2017

AllinaHealth MINNEAPOLIS HEART INSTITUTE

23

FOURIER-OLE

Circulation

Long-Term Evolocumab in Patients with Established Atherosclerotic Cardiovascular Disease

Running Title: *O'Donoghue et al.; Long-term evolocumab in cardiovascular disease*

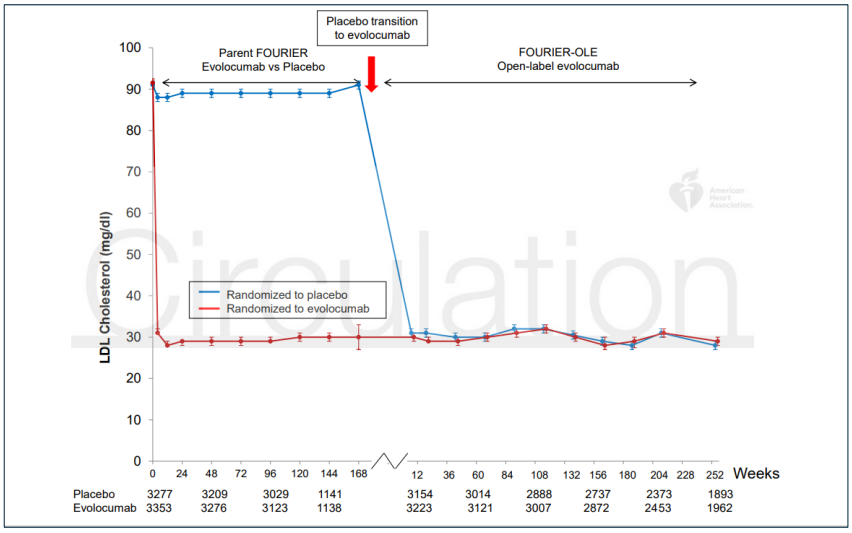
Michelle L. O'Donoghue MD MPH[1]; Robert P. Giugliano MD SM[1]; Stephen D. Wiviott MD[1]; Dan Atar MD[2,3]; Anthony Keech MBBS[4]; Julia F. Kuder MA[1]; KyungAh Im PhD[1]; Sabina A. Murphy MPH[1]; Jose H. Flores-Arredondo MD[5]; J. Antonio G. López MD[5]; Mary Elliott-Davey MSc[6]; Bei Wang PhD[5]; Maria Laura Monsalvo MD[5]; Siddique Abbasi MD[5]; Marc S. Sabatine MD MPH[1]

AllinaHealth MINNEAPOLIS HEART INSTITUTE

FOURIER-OLE, Circulation, 2022

24

LDL Levels Over 5-Years



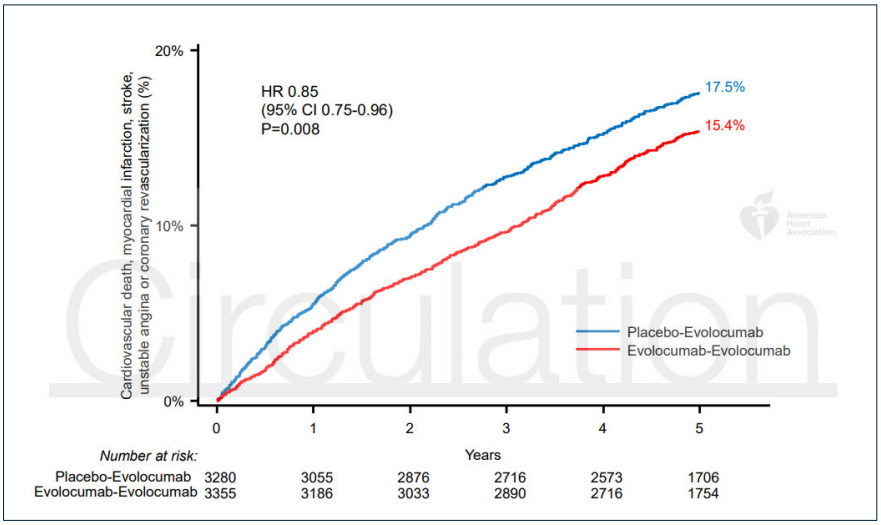
AllinaHealth MINNEAPOLIS HEART INSTITUTE

FOURIER-OLE, Circulation, 2022

25

15% Reduction in Cardiovascular Events

*No Increase in Adverse Events

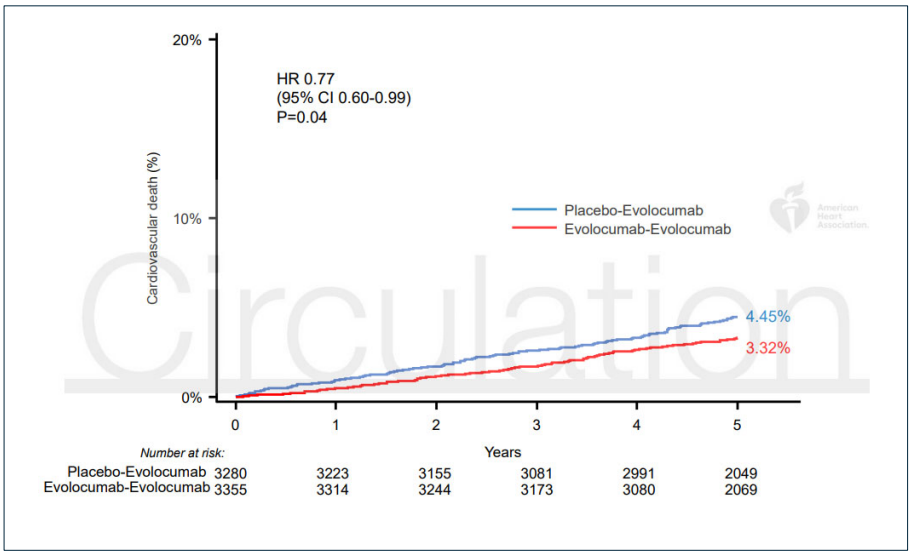


AllinaHealth MINNEAPOLIS HEART INSTITUTE

FOURIER-OLE, Circulation, 2022

26

13% Reduction in Cardiovascular Death



AllinaHealth MINNEAPOLIS HEART INSTITUTE

FOURIER-OLE, Circulation, 2022

27

AMERICAN COLLEGE of CARDIOLOGY

AMERICAN COLLEGE of CARDIOLOGY

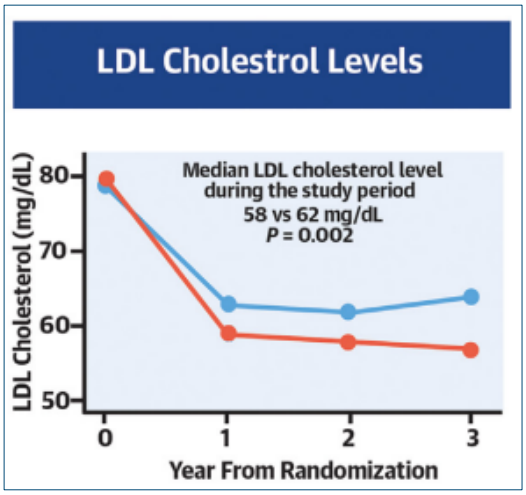
Combination Moderate-Intensity Statin and Ezetimibe Therapy for Elderly Patients With Atherosclerosis

Sang-Hyup Lee, MD,[a,*] Yong-Joon Lee, MD,[a,*] Jung Ho Heo, MD, PhD,[b] Seung-Ho Hur, MD, PhD,[c] Hyun Hee Choi, MD, PhD,[d] Kyung-Jin Kim, MD, PhD,[e] Ju Han Kim, MD, PhD,[f] Keun-Ho Park, MD, PhD,[g] Jung Hee Lee, MD, PhD,[h,i] Yu Jeong Choi, MD, PhD,[j] Seung-Jun Lee, MD, PhD,[a] Sung-Jin Hong, MD, PhD,[a] Chul-Min Ahn, MD, PhD,[a] Byeong-Keuk Kim, MD, PhD,[a] Young-Guk Ko, MD, PhD,[a] Donghoon Choi, MD, PhD,[a] Myeong-Ki Hong, MD, PhD,[a] Yangsoo Jang, MD, PhD,[k] Jung-Sun Kim, MD, PhD[a]

AllinaHealth MINNEAPOLIS HEART INSTITUTE

28

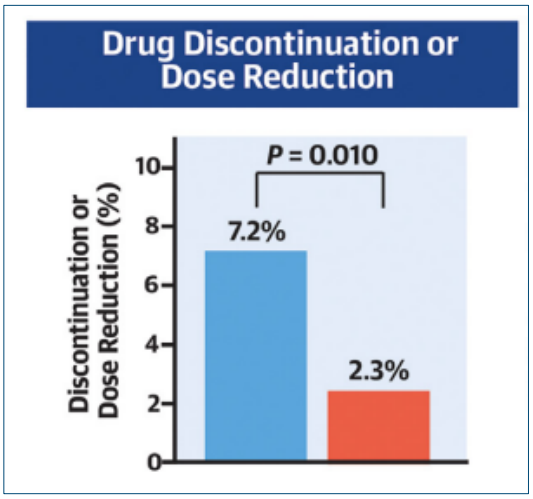
Better LDL lowering with combination therapy



AllinaHealth MINNEAPOLIS HEART INSTITUTE

29

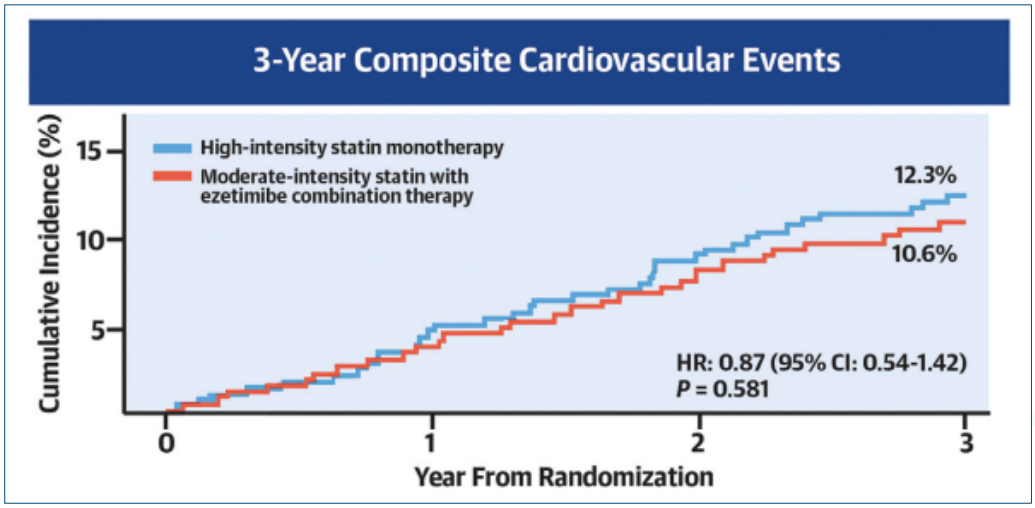
The benefits of combination lipid lowering therapy



AllinaHealth MINNEAPOLIS HEART INSTITUTE

30

The benefits of combination lipid lowering therapy



AllinaHealth MINNEAPOLIS HEART INSTITUTE

31

Current Approach

LDL – as **low** as possible for **long** as possible

Statin → Ezetimibe → PCSK9-i

CVD Risk →

AllinaHealth MINNEAPOLIS HEART INSTITUTE

32

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

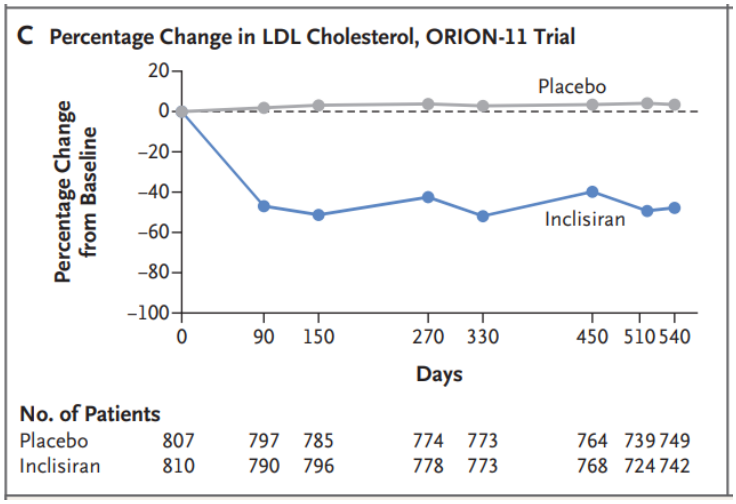
Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol

Kausik K. Ray, M.D., M.Phil., R. Scott Wright, M.D., David Kallend, M.D., Wolfgang Koenig, M.D., Lawrence A. Leiter, M.D., Frederick J. Raal, Ph.D., Jenna A. Bisch, B.A., Tara Richardson, B.A., Mark Jaros, Ph.D., Peter L.J. Wijngaard, Ph.D., and John J.P. Kastelein, M.D., Ph.D., for the ORION-10 and ORION-11 Investigators*

ORION-10+11, NEJM, 2020

33

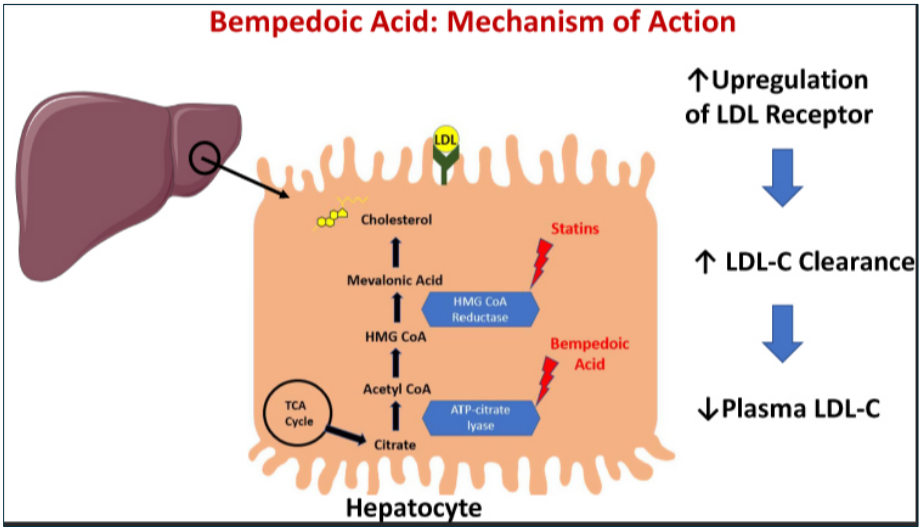
Incliseran lowers LDL-C by ~50%



ORION-10+11, NEJM, 2020

34

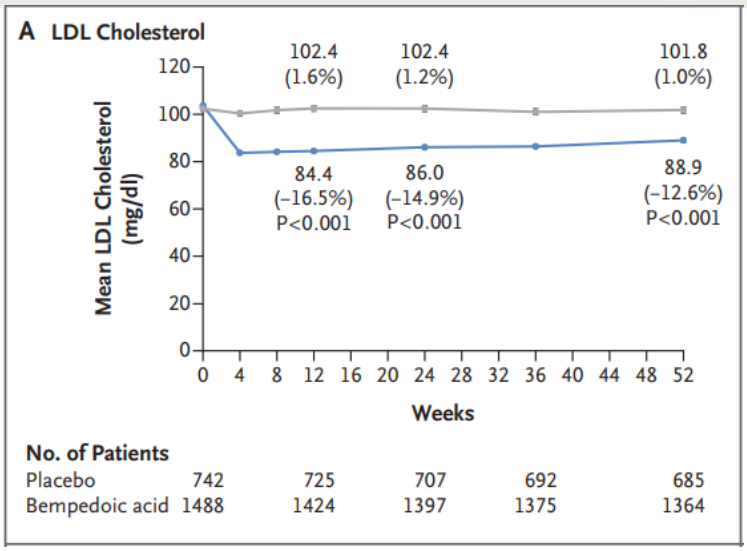
Bempadoic Acid



AllinaHealth MINNEAPOLIS HEART INSTITUTE

35

A ~15% Reduction in LDL-C



AllinaHealth MINNEAPOLIS HEART INSTITUTE

Clear-Harmony, NEJM, 2019

36

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 13, 2023 VOL. 388 NO. 15

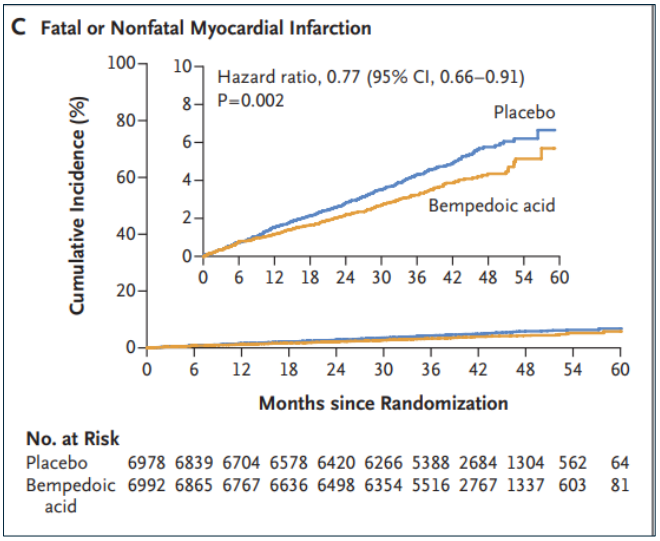
Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

S.E. Nissen, A.M. Lincoff, D. Brennan, K.K. Ray, D. Mason, J.J.P. Kastelein, P.D. Thompson, P. Libby, L. Cho, J. Plutzky, H.E. Bays, P.M. Moriarty, V. Menon, D.E. Grobbee, M.J. Louie, C.-F. Chen, N. Li, L.A. Bloedon, P. Robinson, M. Horner, W.J. Sasiela, J. McCluskey, D. Davey, P. Fajardo-Campos, P. Petrovic, J. Fedacko, W. Zmuda, Y. Lukyanov, and S.J. Nicholls, for the CLEAR Outcomes Investigators*

AllinaHealth MINNEAPOLIS HEART INSTITUTE

37

23% Reduction in fatal and non-fatal MI



AllinaHealth MINNEAPOLIS HEART INSTITUTE

Clear Outcomes – NEJM - 2023

38

The 2022 Kevin Graham Lecture

2022 Kevin Graham Prevention Lecture

From reading the genome for risk to rewriting it for cardiovascular health

Speaker: **Sekar Kathiresan, MD**

CEO, Verve Therapeutics
Cambridge, MA

Learning Objectives

At the completion of this activity, the participants should be better able to:

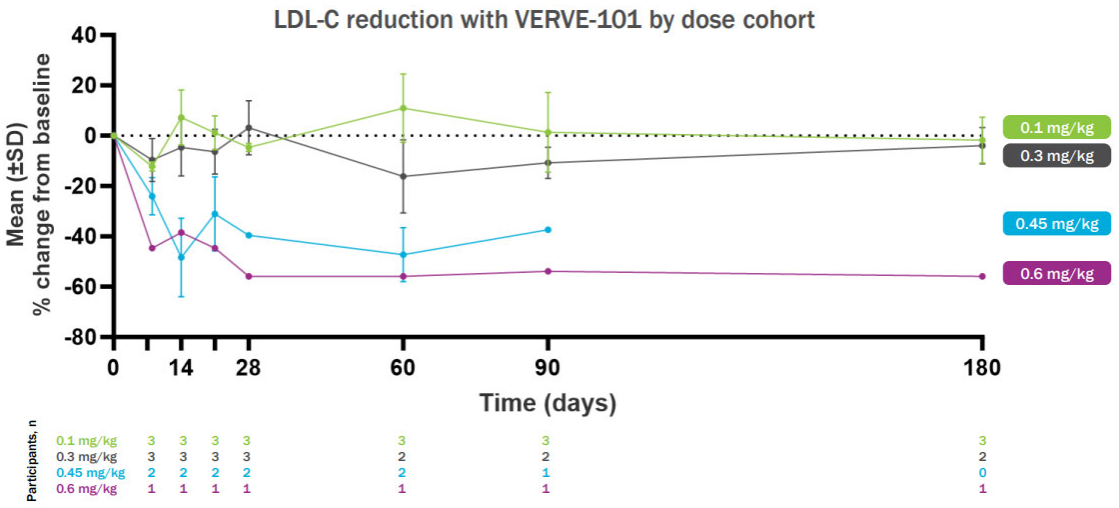
- Name the three major genetic models for myocardial infarction risk – monogentic, polygenic and somatic.
- Describe how natural resistance mutations lower plasma LDL lifelong in some people and lead to protection against heart attack.
- Outline the development of a new class of medicines, which can edit the genome in an adult and lead to permanent lowering of LDL cholesterol after a single treatment.

Minneapolis Heart Institute Foundation Cardiovascular Grand Rounds

Allina Health MINNEAPOLIS HEART INSTITUTE

39

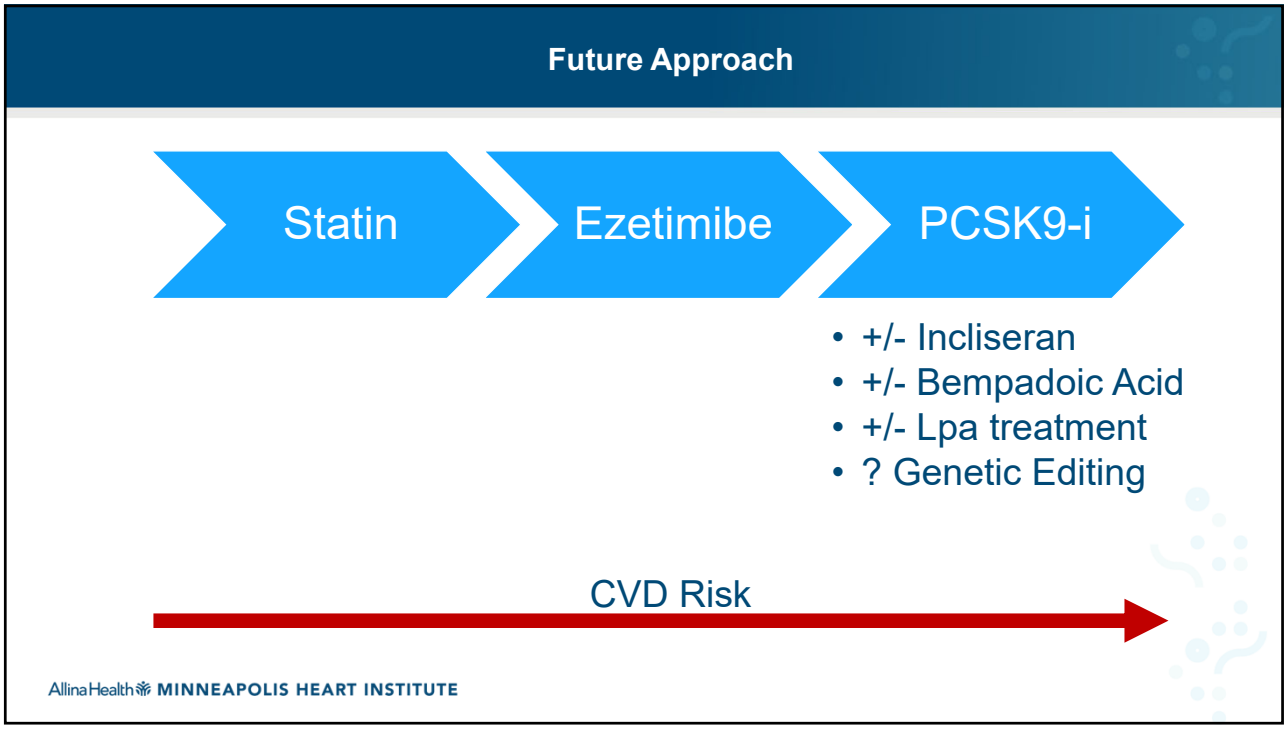
Durable 55% reduction in LDL-C extending up to 180 days in the single participant in the highest dose cohort



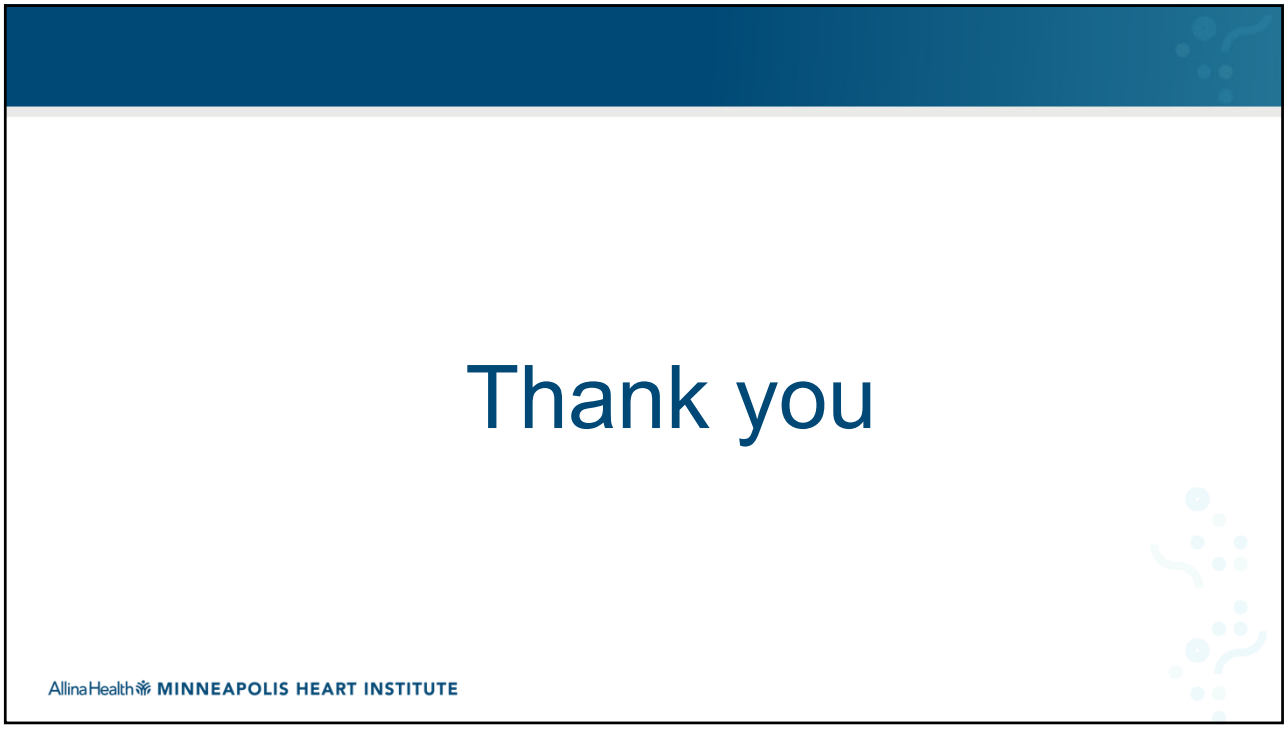
41 As of October 16, 2023. Data are from an ongoing study with an open database and have not been fully cleaned
SD, standard deviation

verve

40


Future Approach
Statin
Ezetimibe
PCSK9-i
• +/- Incliseran
• +/- Bempadoic Acid
• +/- Lpa treatment
• ? Genetic Editing
CVD Risk
Allina Health MINNEAPOLIS HEART INSTITUTE

41


Thank you
Allina Health MINNEAPOLIS HEART INSTITUTE

42

Lipoprotein(a) in Cardiovascular Disease

Felipe V Martignoni, MD
Preventive Cardiology Research Fellow
Nolan Center for Cardiovascular Health, Minneapolis Heart Institute Foundation

PREVENTION
Nolan Family Center for Cardiovascular Health

43

No conflict of interest to disclose.

PREVENTION
Nolan Family Center for Cardiovascular Health

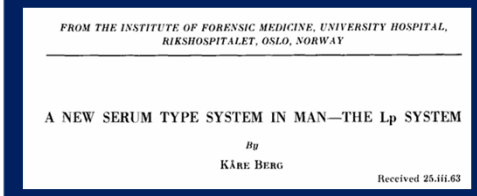
44

Objectives

1) Understand the role of Lp(a) in cardiovascular risk assessment
2) Discuss current and future treatment options

45

History → 1963



FROM THE INSTITUTE OF FORENSIC MEDICINE, UNIVERSITY HOSPITAL, RIKSHOSPITALET, OSLO, NORWAY

A NEW SERUM TYPE SYSTEM IN MAN—THE Lp SYSTEM

By

KÅRE BERG

Received 25.iii.63

An antigenic variant of LDL

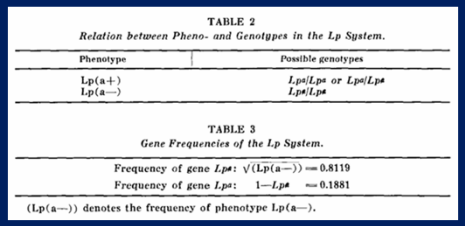


TABLE 2
Relation between Pheno- and Genotypes in the Lp System.

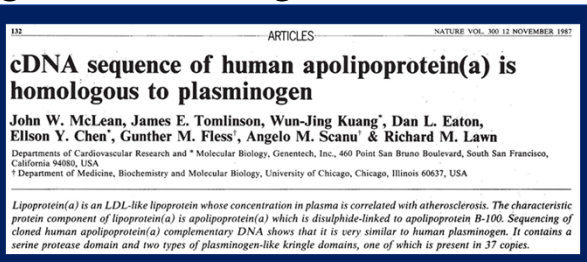
Phenotype	Possible genotypes
Lp(a+) Lp(a—)	*Lp*/Lp** or *Lp*/Lp** *Lp*/Lp**

TABLE 3
Gene Frequencies of the Lp System.

Frequency of gene *Lp**: $\sqrt{(\text{Lp(a—)})} = 0.8119$
Frequency of gene *Lp**: $1 - Lp^* = 0.1881$

(Lp(a—)) denotes the frequency of phenotype Lp(a—).

Apo(a) glycoprotein gene cloning →1987



132 ARTICLES NATURE VOL. 300 12 NOVEMBER 1987

cDNA sequence of human apolipoprotein(a) is homologous to plasminogen

John W. McLean, James E. Tomlinson, Wun-Jing Kuang*, Dan L. Eaton, Ellson Y. Chen*, Gunther M. Fless†, Angelo M. Scanu† & Richard M. Lawn

Departments of Cardiovascular Research and * Molecular Biology, Genentech, Inc., 460 Point San Bruno Boulevard, South San Francisco, California 94080, USA
† Department of Medicine, Biochemistry and Molecular Biology, University of Chicago, Chicago, Illinois 60637, USA

Lipoprotein(a) is an LDL-like lipoprotein whose concentration in plasma is correlated with atherosclerosis. The characteristic protein component of lipoprotein(a) is apolipoprotein(a) which is disulphide-linked to apolipoprotein B-100. Sequencing of cloned human apolipoprotein(a) complementary DNA shows that it is very similar to human plasminogen. It contains a serine protease domain and two types of plasminogen-like kringle domains, one of which is present in 37 copies.

Plasminogen like protein

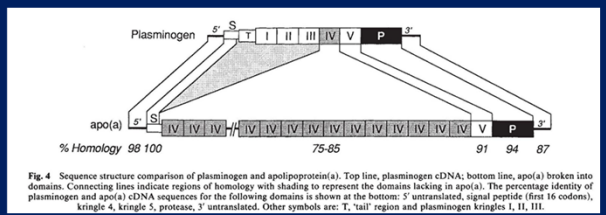
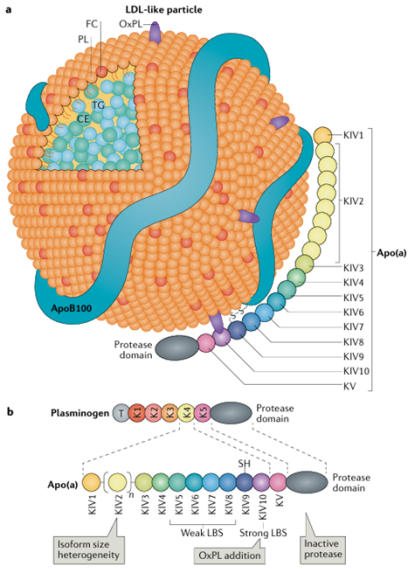


Fig. 4 Sequence structure comparison of plasminogen and apolipoprotein(a). Top line, plasminogen cDNA; bottom line, apo(a) broken into domains. Connecting lines indicate regions of homology with shading to represent the domains lacking in apo(a). The percentage identity of plasminogen and apo(a) cDNA sequences for the following domains is shown at the bottom: 5' untranslated, signal peptide (first 16 codons), kringle 4, kringle 5, protease, 3' untranslated. Other symbols are: T, 'tail' region and plasminogen kringles I, II, III.

46

Lipoprotein (a)

- **LDL-apoB** bound apolipoprotein (a)
- **Risk factor for atherothrombotic** cardiovascular disease and calcific aortic valve disease.
- **Genetically determined-** Does not respond to lifestyle modifications or currently available medications- LPA gene

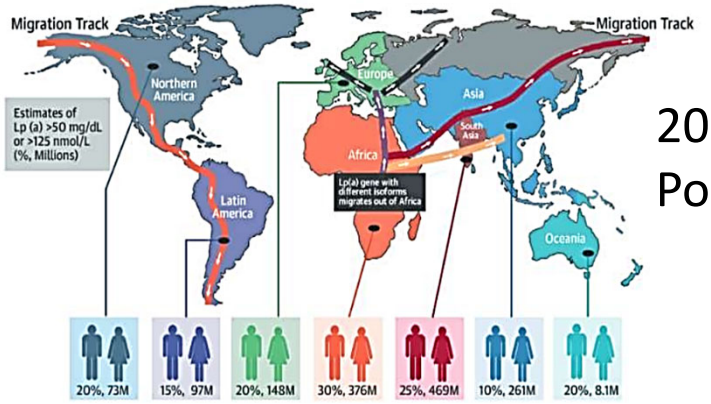


Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

Boffa & Kotchinski 2019- a https://doi.org/10.1038/ s41569-018-0153-2

47

Lp(a) Ethnic Differences



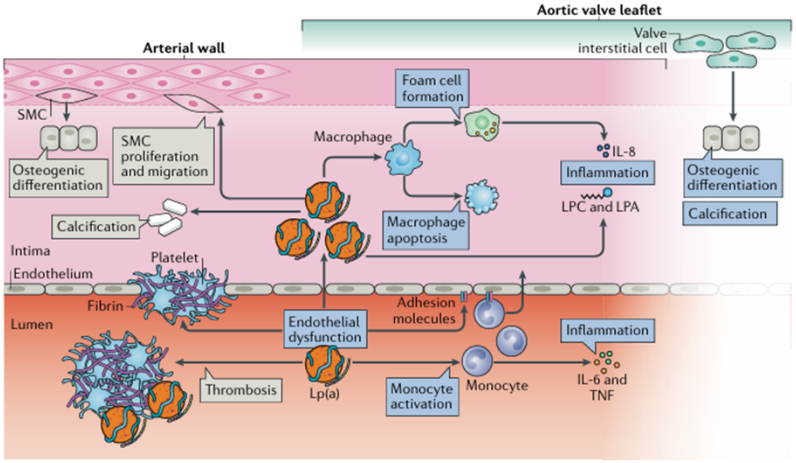
20% of World Population

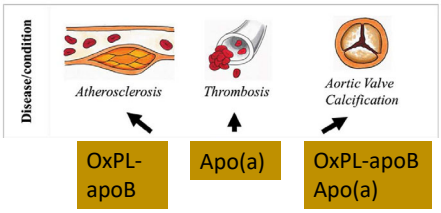
Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

Tsimikas. JACC 2018. 71(2):177-192

48

Pathophysiology





Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

Arterioscler Thromb Vasc Biol. 2022 Jan; 42(1): e48–e60

Boffa & Kotchinski 2019- a https://doi.org/10.1038/ s41569-018-0153-2

49

Evidence Linking Lp(a) to Atherosclerosis

Table 1. Landmark Studies Linking Lipoprotein(a) (Lp[a]) to Cardiovascular Disease

Source	Design	Population	Key findings
Association between Lp(a) and ASCVD			
CCHS[25]	Prospective	9330 Individuals from the general population in Denmark	Adjusted HR for incident myocardial infarction with Lp(a) levels ≥120 mg/dL (≥95th percentile) vs levels <5 mg/dL (<22nd percentile) were 3.6 (95% CI, 1.7-7.7) in women and 3.7 (95% CI, 1.7-8.0) in men
Emerging Risk Factors Collaboration[4]	Meta-analysis	126 634 Individuals with no prior history of coronary heart disease or stroke from 36 cohorts	Adjusted RR of 1.13 (95% CI, 1.09-1.18) for incident coronary heart disease per 1-SD rise in Lp(a)
Kamstrup et al,[8] 2009	Mendelian randomization	40 486 Patients from 3 large Danish cohorts: CCHS, CGPS, and CIHS	Causal association between increasing genetically determined Lp(a) levels and the risk of myocardial infarction (HR per doubling of Lp[a] levels, 1.22; 95% CI, 1.09-1.37)
O'Donoghue,[26] 2014	Meta-analysis	18 978 Individuals with coronary artery disease	OR for MACE was 1.40 (95% CI, 1.15-1.71) for the highest vs lowest Lp(a) quantile
UK Biobank[3]	Prospective	460 506 Middle-aged individuals with and without ASCVD	Incident or recurrent ASCVD events had an overall HR of 1.11 (95% CI, 1.10-1.12) per 50-nmol/L increment in Lp(a) concentrations
Association between lipoprotein(a) and calcific aortic valve stenosis			
CCHS and CGPS[5]	Mendelian randomization	77 680 Danish participants from the general population	When combining all genotypes, a genetic RR for aortic stenosis of 1.6 (95% CI, 1.2-2.1) for a 10-fold increase in Lp(a) concentration was reported
EPIC-Norfolk[6]	Prospective	17 553 Adults from the general UK population	Participants in the top Lp(a) tertile had an adjusted HR for aortic stenosis of 1.57 (95% CI, 1.02-2.42) compared with participants in the bottom tertile
FOURIER[27]	Clinical trial	27 564 Individuals with stable ASCVD taking statins	The adjusted HR for aortic stenosis events was 1.55 (95% CI, 1.17-2.05) per 1-SD increase in Lp(a) levels; LDL-C levels had no association with aortic stenosis
Association between Lp(a) and ischemic stroke			
Emerging Risk Factors Collaboration[4]	Meta-analysis	126 634 Individuals with no prior history of coronary heart disease or stroke from 36 cohorts	Adjusted RR for ischemic stroke was 1.10 (95% CI, 1.02-1.18) per 1-SD rise in Lp(a)
CCHS and CGPS[28]	Prospective	60 512 Individuals from the general Danish population	The HR for ischemic stroke was 1.60 (95% CI, 1.24-2.05) for individuals with Lp(a) >93 mg/dL compared with individuals with Lp(a) <10 mg/dL

ESC European Society of Cardiology | European Journal of Preventive Cardiology (2024) 00, 1–10 https://doi.org/10.1093/eurjpc/zwae043

FULL RESEARCH PAPER
Cardiovascular disease

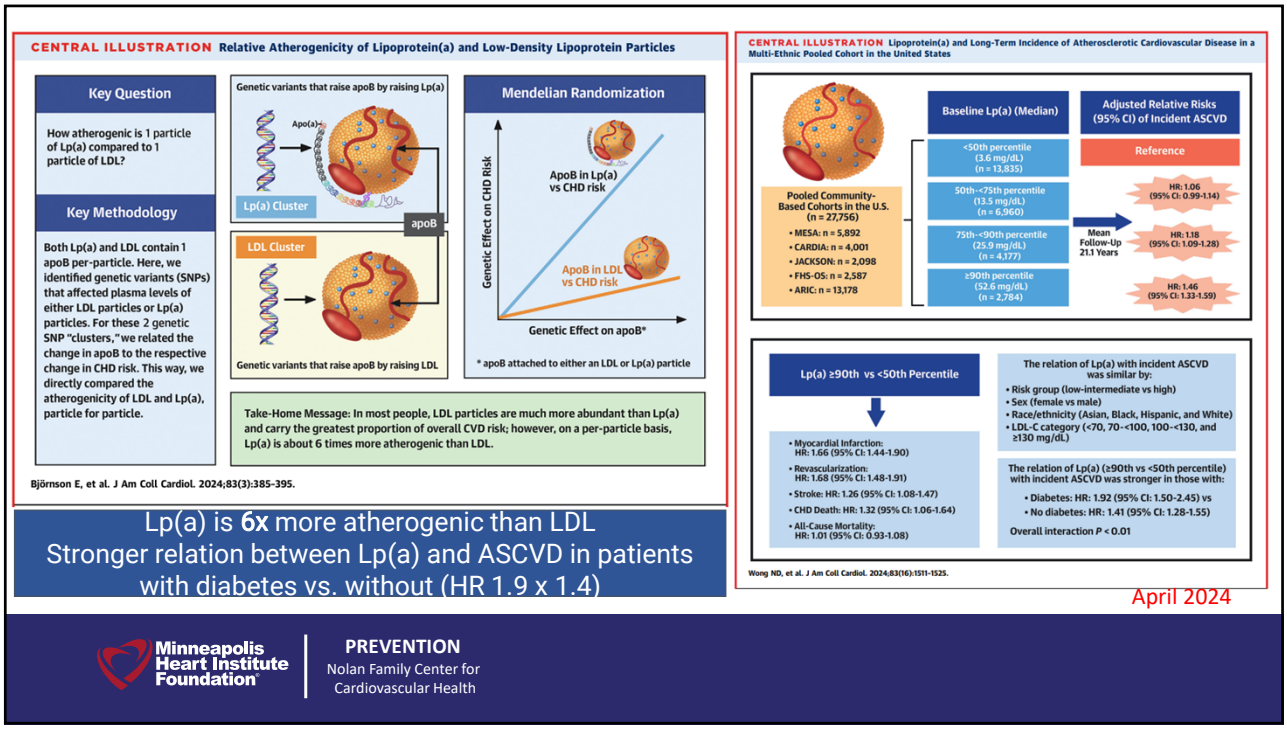
The association of lipoprotein(a) and coronary artery calcium in asymptomatic patients: a systematic review and meta-analysis

Felipe Villa Martignoni [1]*, José Eduardo RL Júnior[2], Isabela R. Marques[3], Cintia Gomes[4], Vittoria Caporal S. Moreira[5], Isabela A. F. de Souza[6], Isabele A. Miyawaki[7], Caroliny H. Silva[8], Augusto Barreto do Amaral Neto[9], Eduardo M. H. Padrão[10], Rhanderson Cardoso [11], Henrique Doria de Vasconcellos[12], and Michael Miedema[1]

Eur J Prev Cardiol. 2024 Feb 1:zwae043.

JAMA Cardiology July 2022 Volume 7, Number 7

50

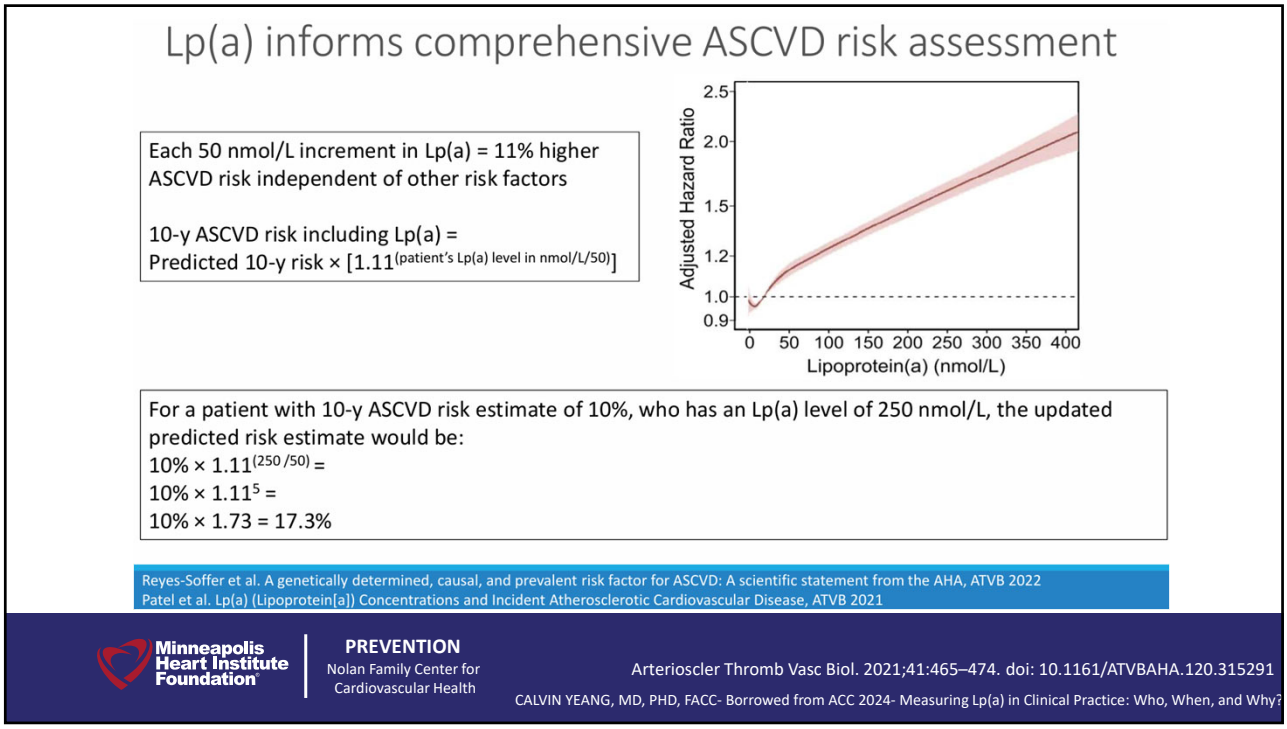


Lp(a) is **6x** more atherogenic than LDL
Stronger relation between Lp(a) and ASCVD in patients with diabetes vs. without (HR 1.9 x 1.4)

April 2024

Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

51



Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

Arterioscler Thromb Vasc Biol. 2021;41:465–474. doi: 10.1161/ATVBAHA.120.315291

CALVIN YEANG, MD, PHD, FACC- Borrowed from ACC 2024- Measuring Lp(a) in Clinical Practice: Who, When, and Why?

52

Estimates of Risk Reduction LDL vs Lp(a)

22% risk reduction after LDL reduction of **40 mg/dL**

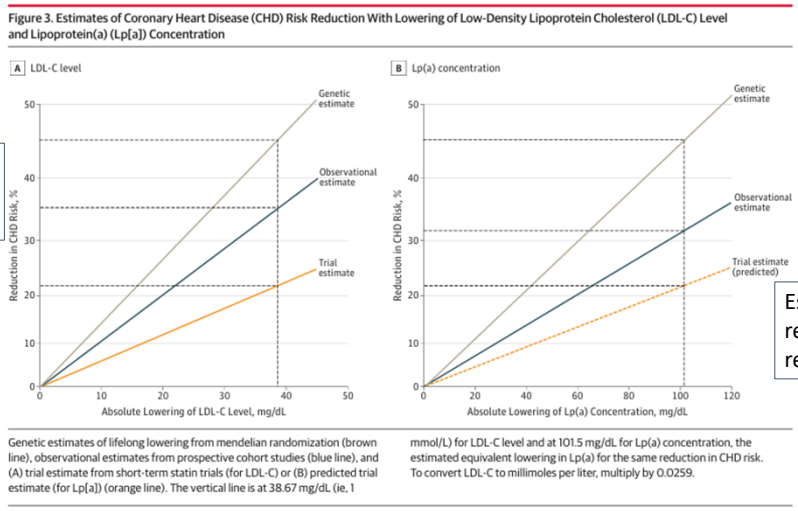


Figure 3. Estimates of Coronary Heart Disease (CHD) Risk Reduction With Lowering of Low-Density Lipoprotein Cholesterol (LDL-C) Level and Lipoprotein(a) (Lp[a]) Concentration

Genetic estimates of lifelong lowering from mendelian randomization (brown line), observational estimates from prospective cohort studies (blue line), and (A) trial estimate from short-term statin trials (for LDL-C) or (B) predicted trial estimate (for Lp[a]) (orange line). The vertical line is at 38.67 mg/dL (ie, 1 mmol/L) for LDL-C level and at 101.5 mg/dL for Lp(a) concentration, the estimated equivalent lowering in Lp(a) for the same reduction in CHD risk. To convert LDL-C to millimoles per liter, multiply by 0.0259.

Estimated **22%** risk reduction after Lp(a) reduction of **100 mg/dL**

Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

JAMACardiol. 2018;3(7):619-627. doi:10.1001/jamacardio.2018.1470

53

Non-genetic influences on Lp(a) levels

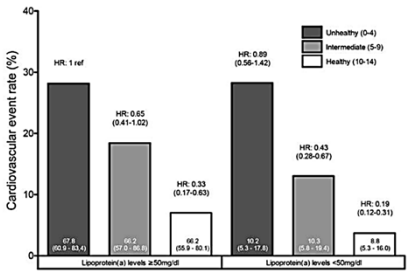
Condition	Effect on Lp(a) levels
Medical Conditions	
Advanced CKD	Increase in those with large apo(a) isoforms
Nephrotic syndrome	3-5 times higher than controls
Liver transplant recipient	Lp(a) levels reflect that of donor
Acute MI	Variable, no change or increase
Severe inflammatory conditions	Increase
Hormonal	
Thyroid disorder	Increase with hypothyroidism; decrease with hyperthyroidism
Pregnancy	Increase
Menopause	Minimal
Pituitary insufficiency	~2x increase with growth hormone treatment
Medications	
Statins	Variable, no change or increase
PCSK9i	~10-30% decrease
Postmenopausal hormone replacement therapy	~25% decrease

Adapted from Kronenberg et al, Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement, European Heart Journal 2022

Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

54

Actionable strategies in patients with high Lp(a)



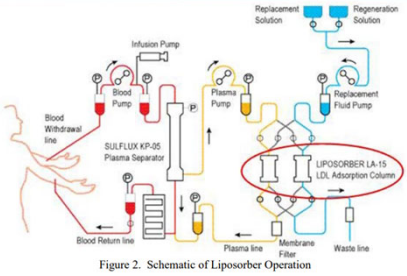
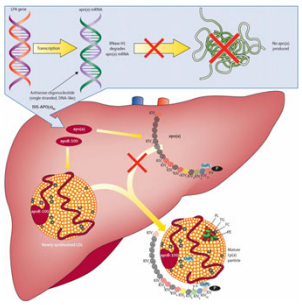


Figure 2. Schematic of Liposorber Operation



Lifestyle Modifications

Lipid Lowering therapy (PCSK-9?)

Niacin, Aspirin (?)

Lp(a) Apheresis

Effective, but cumbersome

FDA approved

Exploring Lp(a) Targeted Therapy

Phase III Results are coming

Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

Perrot et al. Atherosclerosis 2017

55

The Benefit of PCSK9 Therapy is Dependent on Lp(a)

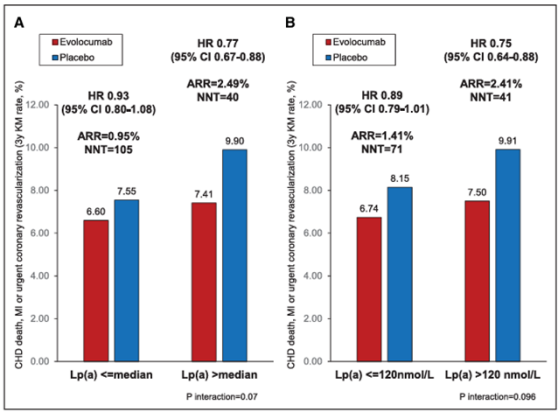


Figure 1. The efficacy of Evolocumab by Lp(a) concentration split at the median (A) and split at 120 nmol/L (50 mg/dL) for reducing CHD (B).

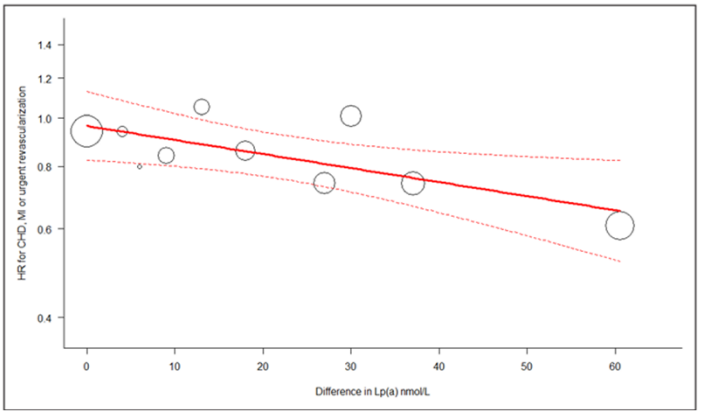


Figure 2. Treatment effect on major coronary events per unit decrease in Lp(a).

Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

Circulation. 2019;139:1483–1492.

56

Lp(a) targeted CVOT Outcomes Trial

Anti Sense Oligonucleotides (ASO)

PelacarSEN → Lp(a) Horizon

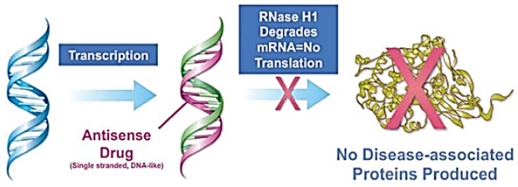
Small Interfering RNA

OlpaSIRan → Ocean(a)

Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

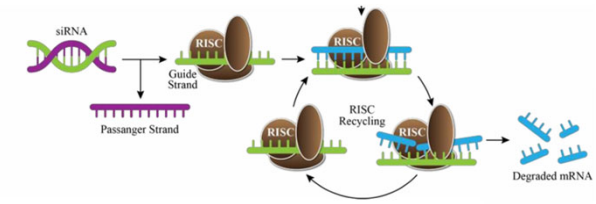
57

Antisense Oligonucleotide Blocks Translation of Disease-Causing Protein by Targeting mRNA



Antisense oligonucleotides (ASOs) are small, synthetic pieces of RNA that can bind to specific RNA molecules. This prevents translation of Apo(a).

Small Interfering RNA



RNA-induced silencing complex, or RISC-Multiprotein complex that incorporates one strand of a siRNA. RISC uses the siRNA as a template for recognizing complementary mRNA. When it finds a complementary strand, it activates RNase and cleaves the RNA.

Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

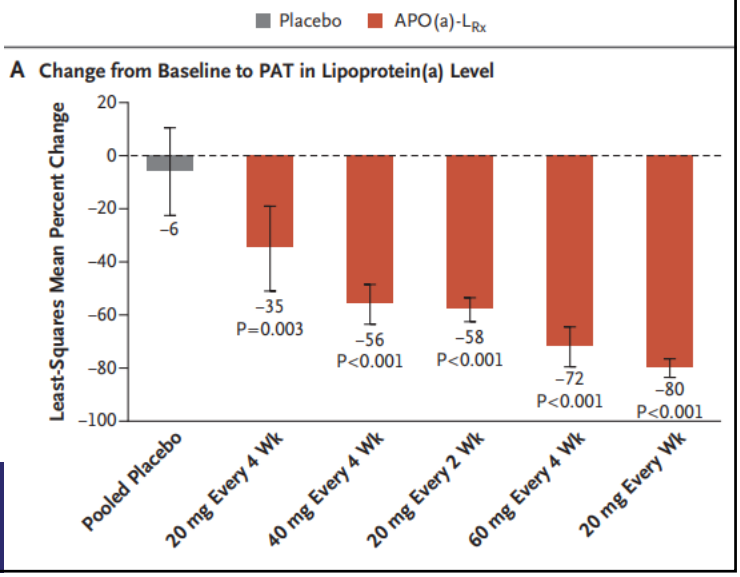
58

Effect of APO(a)-L_{Rx} on Lp(a) Levels

ORIGINAL ARTICLE

Lipoprotein(a) Reduction in Persons with Cardiovascular Disease

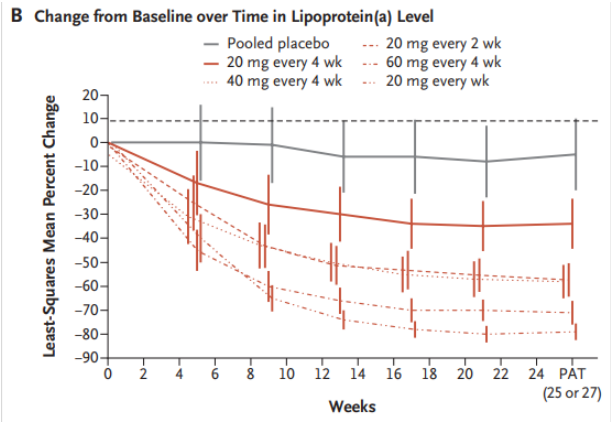
Sotirios Tsimikas, M.D., Ewa Karwatowska-Prokopczuk, M.D., Ph.D., Ioanna Gouni-Berthold, M.D., Jean-Claude Tardif, M.D., Seth J. Baum, M.D., Elizabeth Steinhagen-Thiessen, M.D., Michael D. Shapiro, D.O., Erik S. Stroes, M.D., Patrick M. Moriarty, M.D., Børge G. Nordestgaard, M.D., D.M.Sc., Shuting Xia, M.S., Jonathan Guerriero, M.B.A., Nicholas J. Viney, B.Sc., Louis O'Dea, M.B., B.Ch., B.A.O., and Joseph L. Witztum, M.D., for the AKCEA-APO(a)-L_{Rx} Study Investigators*

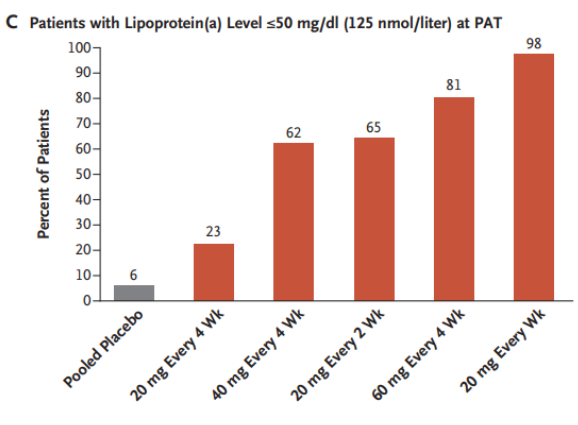


Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

59

Effect of APO(a)-L_{Rx} on Lp(a) Levels





Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

Tsimikas et al., N EnglJ Med 382;3 Nejm.org January 16, 2020

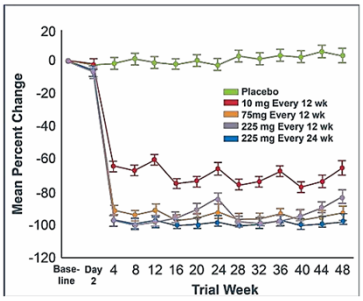
60

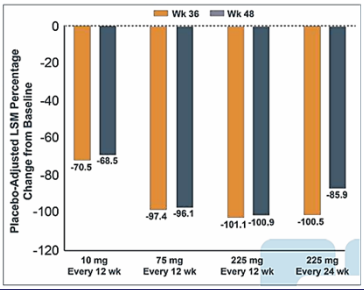
Effect of Olpasiran on Lp(a) Levels

ORIGINAL ARTICLE

Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease

Michelle L. O'Donoghue, M.D., M.P.H., Robert S. Rosenson, M.D., Baris Gencer, M.D., M.P.H., J. Antonio G. López, M.D., Norman E. Lepor, M.D., Seth J. Baum, M.D., Elmer Stout, M.D., Daniel Gaudet, M.D., Ph.D., Beat Knusel, Ph.D., Julia F. Kuder, M.A., Xinhui Ran, M.S., Sabina A. Murphy, M.P.H., Huei Wang, Ph.D., You Wu, Ph.D., Helina Kassahun, M.D., and Marc S. Sabatine, M.D., M.P.H., for the OCEAN(a)-DOSE Trial Investigators*





Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

O'Donoghue et al., N Engl J Med 2022;387:1855-64. DOI: 10.1056/NEJMoa2211023

61

Phase 3 study CVOT RCT Comparison

- Lp(a) HORIZON
- 12/12/2019 – finished enrolling 2022
- Once a month injection Pelacarsen (ASO) vs. placebo
- 8000+ patients s/p MI >3 month < 10 years
- Lp(a) > 70mg/dL (≈165nmol/L)
- F/u ≈ 5 years

- OCEAN(a)
- 01/2023
- Q3 month injection Olpasiran (siRNA) vs. placebo
- 6000+ patients- MI - PCI +1 risk factor
- Lp(a) > 200 nmol/L (≈ 100 mg/dL)
- f/u ≈ 4 years

Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

62

Guidelines on Testing for Lp(a)

Box. When to Measure Lipoprotein(a) (Lp[a]) and Thresholds for Treatment

2018 American College of Cardiology/American Heart Association Cholesterol Guidelines[19]
- ASCVD not explained by major risk factors
- Family history of premature ASCVD[a]
- Lp(a) levels ≥125 nmol/L (≥50 mg/dL) are considered an ASCVD risk-enhancing factor

2019 HEART UK Consensus Statement[22]
- Personal or family history of premature ASCVD[c]
- First-degree relatives with serum Lp(a) levels >200 nmol/L
- Familial hypercholesterolemia or other genetic dyslipidemias
- Calcific aortic valve stenosis
- Borderline increased (but <15%) 10-year ASCVD risk
- Lp(a) levels >90 nmol/L are considered high risk

2020 Endocrine Society Lipid Management Guidelines[23]
- Family history of premature ASCVD or high Lp(a)
- Personal history of ASCVD
- Lp(a) levels ≥125 nmol/L (≥50 mg/dL) are considered an ASCVD risk-enhancing factor

2019 National Lipid Association Scientific Statement[20]

2019 European Society of Cardiology/European Atherosclerosis Society Guidelines for the Management of Dyslipidaemias[21]

2021 Canadian Guidelines for the Management of Dyslipidemia[24]

Recommendations
- Adults (aged ≥18 y): Measurement of Lp(a) in all adults

April 2024

Universal Screening

Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

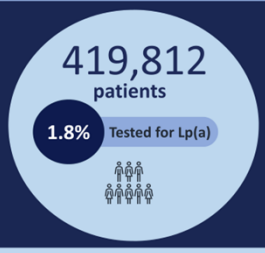
JAMA Cardiol. 2022;7(7):760-769.

Journal of Clinical Lipidology (2024) 000, 1–12

63

Real World Data Allina System

Figure 1. Prevalence of Lp(a) testing and baseline demographics in adults 40-79 years from 2004-2023.



- Median age 61
- 52% female
- 90% white
- 61% dyslipidemia
- 11% ASCVD

Lp(a) was tested in 1.8% of the total sample, including 1.4% of those without prior ASCVD and 4.9% of patients with ASCVD (Figure 1).

Characteristics	Total population 419,813[1]	No ASCVD 371,744[1]	ASCVD 48,069[1]	p-value[2]
Age	61 (52- 70)	60 (51-69)	69 (61-75)	p<0.01
Female	218,205 (52%)	201,041 (54%)	17164 (36%)	p<0.01
White	375,884 (90%)	331,853 (89%)	44,031 (92%)	p<0.01
BMI	29 (25, 34)	29 (25-34)	30 (26-34)	p<0.01
Dyslipidemia	256,665 (61%)	212, 977 (55%)	43,668 (91%)	p<0.01
Diabetes	81,401 (19%)	62,971 (17%)	18,430 (38%)	p<0.01
Hypertension	223,228 (53%)	181,501 (49%)	41,727 (87%)	p<0.01
Tobacco Status				
Every Day/Some Day	47,881 (11.4%)	41,165 (11%)	6,755 (14%)	p<0.01
Former	141,755 (34%)	118,978 (32%)	22,777(47%)	p<0.01
Collected Lp(a)	7,619 (1.8%)	5,260 (1.4%)	2,359 (4.9%)	p<0.01
mg/dL	-	20 (8,55)	27 (10,76)	p=0.015
nmol/L	-	47 (19-129)	59 (20-174)	p<0.01
Elevated Lp(a)	-	1,410 (27%)	846 (36%)	p<0.01

[1]Median (IQR); n (%); BMI: body mass index;
[2]Pearson's Chi-Squared; Wilcoxon rank sum test

Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

64

Allina Data

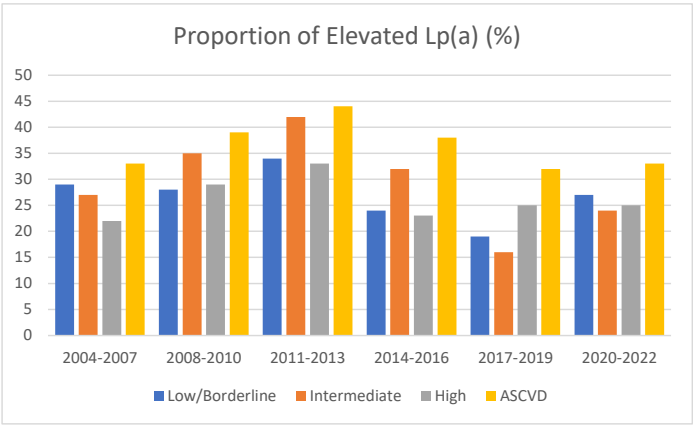
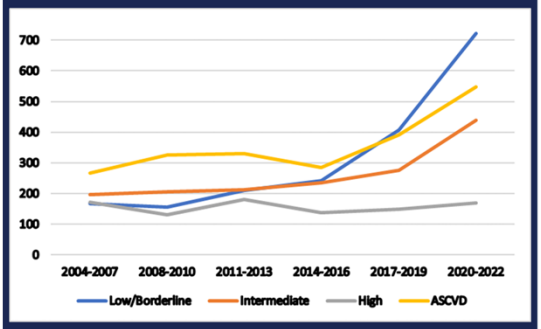


Figure 2. Prevalence of Lp(a) testing according to ASCVD risk status from 2004-2023 in a large Midwest healthcare system.



While the prevalence of Lp(a) testing was low, there has been a recent increase in Lp(a) testing (Figure 2).

Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

65

Allina Outcomes

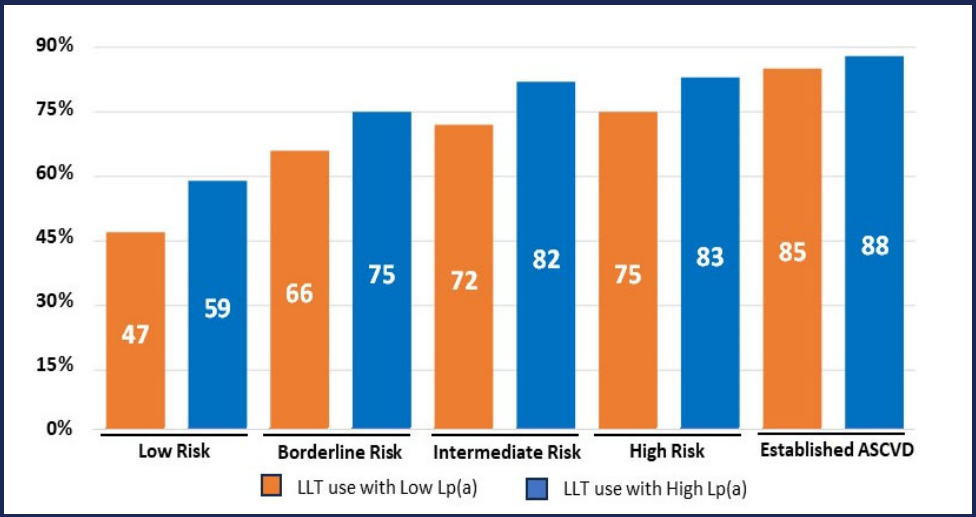
30% of patients had elevated Lp(a)

59% of patients had a variance of **> 20%** from consecutive measurements.

Minneapolis Heart Institute Foundation | PREVENTION Nolan Family Center for Cardiovascular Health

66

Use of LLT in 7,618 patients who underwent Lp(a) testing according to Lp(a) elevation and ASCVD risk status.



67

Allina Health

TRENDS IN CARDIOVASCULAR RISK FACTORS AND USE OF PREVENTIVE CARDIOVASCULAR MEDICATIONS IN PATIENTS PRESENTING WITH ST-ELEVATION MYOCARDIAL INFARCTION

Minneapolis Heart Institute Foundation

Felipe Martignoni MD PhD[1], Hayley Turch DO[1], Timothy Henry[2], Marc Newell[1], Ellen Cravero MS[1], Larissa Stanberry PhD[1], Michael Miedema MD MPH[1]

1. Minneapolis Heart Institute Foundation, Minneapolis MN
2. The Christ Hospital, Cincinnati OH

INTRODUCTION

ST-elevation myocardial infarction (STEMI) is a severe manifestation of potentially preventable cardiovascular (CVD) disease.

Statins, antihypertensives, and antiplatelet agents lower CVD risk but are often underused.

AIM

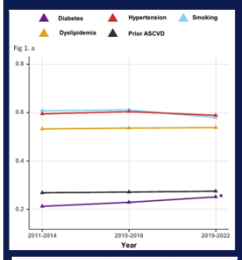
To assess the prevalence of CVD risk factors and use of preventive CVD medications over the past 10+ years in a large Midwest STEMI system.

METHODS

Analysis: Consecutive STEMI patients from the Level One STEMI program at the Minneapolis Heart Institute between 2003 and 2023.

Variables collected: Baseline demographics, traditional CVD risk factors, and pre-admission CVD medications.

Prevalence of CVD risk factors and use of preventive CVD medications during 2011-14, 2015-2018, and 2019-2022 in 7,854 STEMI patients



Pearson's Chi-Squared;
*p<0.05, comparing 2011-14 to 2019-22

7,854
first-time STEMI patients

Table 1. Baseline Characteristics

Characteristics	Total population 7,854
Age	64 (54, 74)
Female	2,369 (30%)
White	7,111 (93%)
Dyslipidemia	4,138 (54%)
Diabetes	1,617 (20%)
Hypertension	4,569 (59%)
Smoker	2,465 (32%)
Prior CVD	2,013 (27%)

Abbreviations:
- ACE-i: Angiotensin-converting enzyme inhibitor
- ARB: Angiotensin receptor blocker
- ASCVD: Atherosclerotic Cardiovascular Disease

RESULTS

The sample (n=7,854) was relatively young (mean age 64 years) with a high prevalence of dyslipidemia (54%) and hypertension (59%). (Table 1)

More than 70% of STEMI patients had no prior ASCVD, which has remained stable over the past decade (Figure 1a).

Comparing 2011-14 to 2019-22, there were no significant changes in the prevalence of smoking, hypertension, prior CVD, or dyslipidemia, but diabetes increased from 21% to 25% (p=0.012) (Figure 1a).

In those without prior CVD, statin use prior to STEMI increased from 19% to 29% (p<0.01), ACE-i/ARB from 19% to 29% (p<0.01), and beta-blockers from 17% to 22% (p<0.05), with a non-significant decline in use of aspirin. Secondary prevention statin increased from 64% to 75% (p<0.01), with no change in other medications, including aspirin (Figure 1b).

CONCLUSIONS

- **In a sample of >7,800 patients with STEMI, >70% had no clinical ASCVD prior to STEMI, which has remained unchanged over time**
- **The prevalence of traditional CVD risk factors prior to STEMI has remained stable except for a slight increase in diabetes**
- **Utilization of preventive CVD medications remains suboptimal, especially in primary prevention.**
- **Better methods of CVD risk assessment and implementation of current guidelines are needed.**

68

Questions?

Why varying so much?

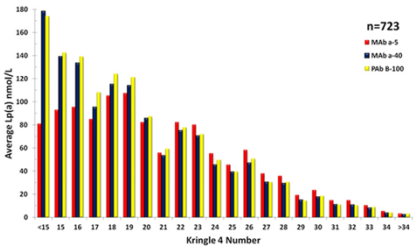


Fig. 2. Comparison of Lp(a) values obtained by ELISA using the same MAb (a-6) to capture Lp(a) in the samples and different detecting MAbs (a-5 and a-40) and a polyclonal antibody to B-100. Mean Lp(a) levels obtained by each detecting antibody were compared as a function of the predominantly expressed apo(a) isoform size.