Practical Updates in Primary Care

Enhancing Cardiovascular Health through Lipid Management: Non-Statin Therapeutics for Effective Risk Reduction

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Disclosures

- **Seth S. Martin, MD, MHS, FACC, FAHA, FASPC:** Grant/Research Support – Amgen, Merck, NewAmsterdam; Advisory Board – Amgen, Arrowhead, AstraZeneca, Heartflow, Merck, NewAmsterdam Pharma, Novartis, Verve Therapeutics; Consultant – Amgen, Arrowhead, AstraZeneca, Chroma, Heartflow, Kaneka, Merck, NewAmsterdam Pharma, Novartis, Verve Therapeutics

- **Daniel E. Soffer, MD:** Grant/Research Support – Amgen, Amryt Pharma; Consultant – Ionis Pharmaceuticals; Speaker's Bureau – Ionis Pharmaceuticals; Advisory Board – NewAmsterdam Pharma, Regeneron; Sub-Investigator – Akcea, Amgen, Amryt Pharma, Arrowhead, Heartflow, Ionis Pharmaceuticals, Lilly, Novartis

Learning Objectives

- Apply guideline-directed strategies for the screening and assessment of elevated LDL-C to optimize early identification, risk stratification, and ASCVD outcomes
- Evaluate the safety and efficacy of newer and emerging non-statin therapeutics to reduce LDL-C in patients with or at risk of developing ASCVD
- Describe treatment intensification strategies and the utility of combination therapies for achieving LDL-C goals
- Implement evidence-based approaches to improve patient adherence to LDL-C-lowering therapies and optimize long-term CV risk reduction

LDL-C = low-density lipoprotein cholesterol; ASCVD = atherosclerotic cardiovascular disease.

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Section 1: Overview of LDL/ApoB and ASCVD

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Past-President, National Lipid Association, 2023/24

Key Points

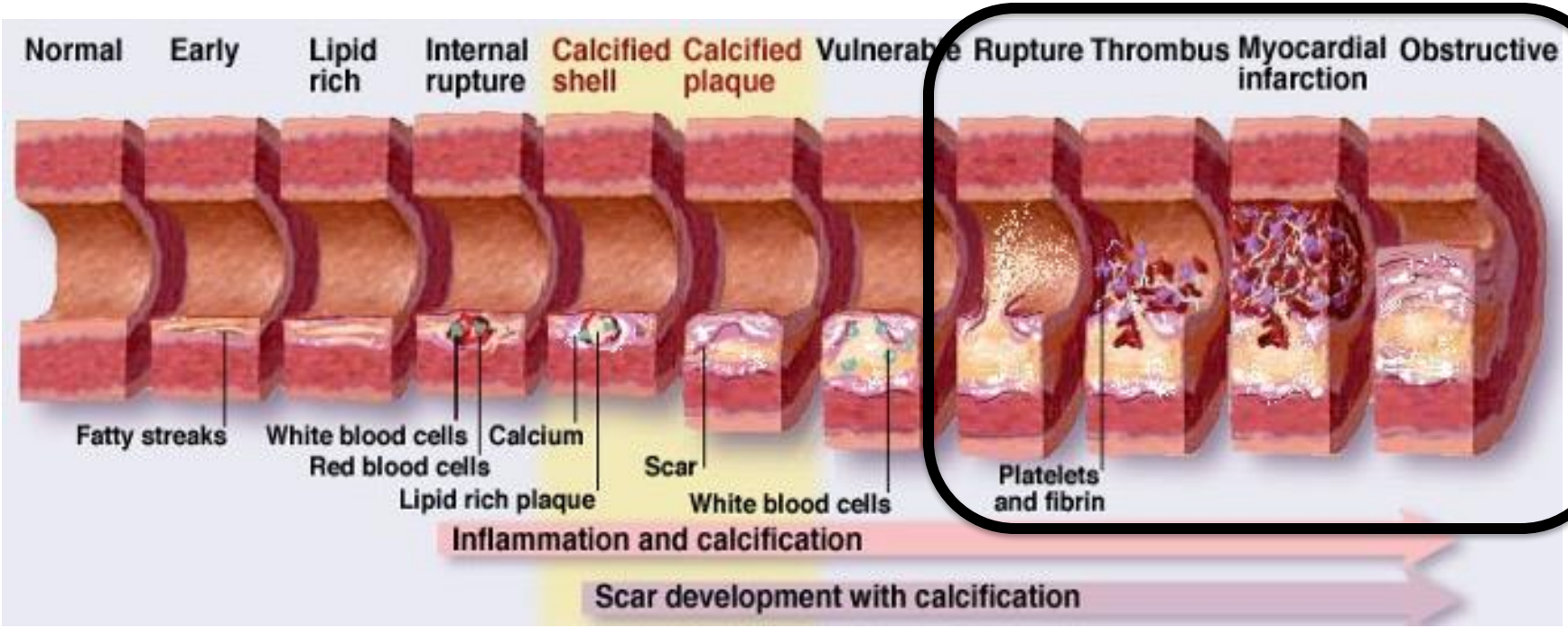
1. Plaque is **silent** until blood flow is compromised (gradual vs sudden)

2. Risk factors promote plaque formation

3. **LDL** is building block for plaque

4. **Treatment** of risk factors (LDL, *et al*) affects CV outcomes

Atherosclerosis Timeline



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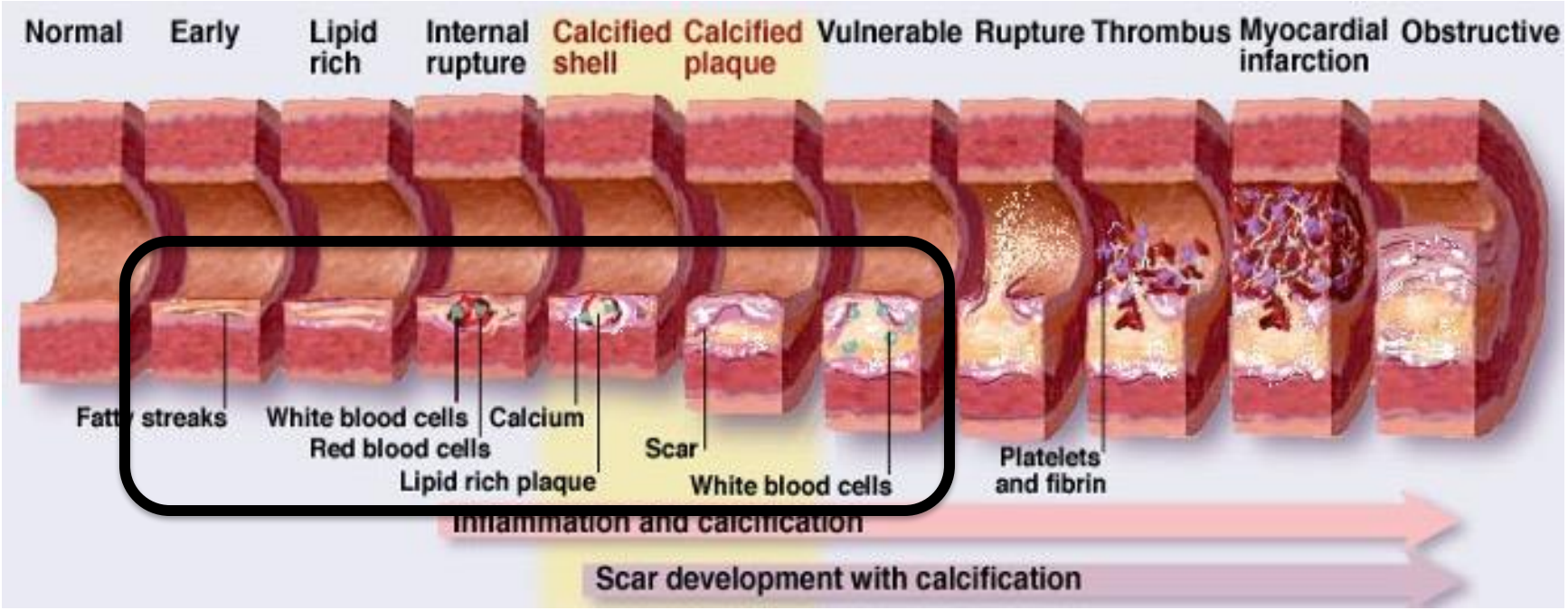
Atherosclerosis Timeline



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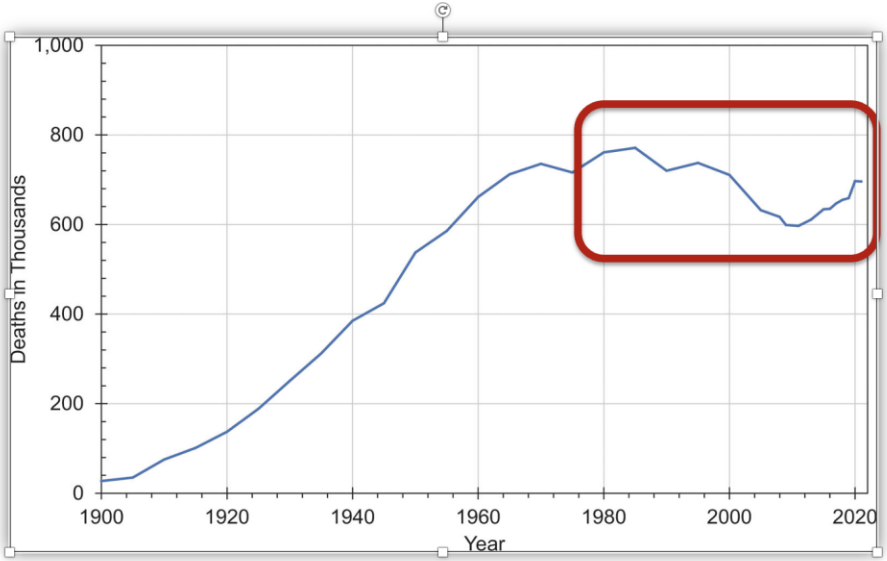
Deaths Attributable to Heart Disease: 1900-2022

Rising HD deaths offset by innovation and public health attention

Acute	Chronic, Medical
CPR (cardiopulmonary resuscitation) Defibrillators CABG (coronary artery bypass grafting) CCU (cardiac care unit) Coronary angiography PTCA (percutaneous transcatheter coronary angioplasty) Thrombolytics Coronary stenting Door-to-ballon hs-Troponin	Beta-blockers RAAS (renin-angiotensin-aldosterone) inhibitors Statins High-intensity statins Ezetimibe DAPT (dual anti-platelet therapy) PCSK9i



HD = heart disease.

Martin SS, et al. *Circulation*. 2025;151(8):e41-e660.

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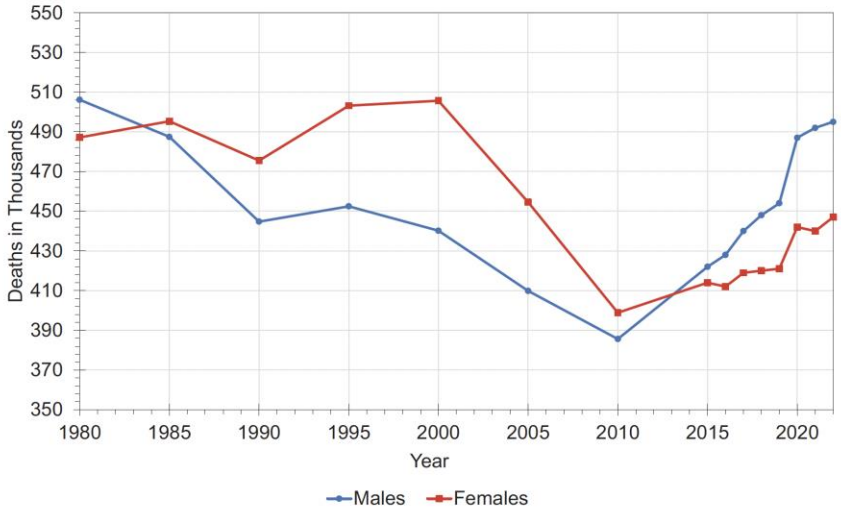
CVD Mortality in US: 1980-2022 (Males, Females)

Public health success beaten back by changing demographic...

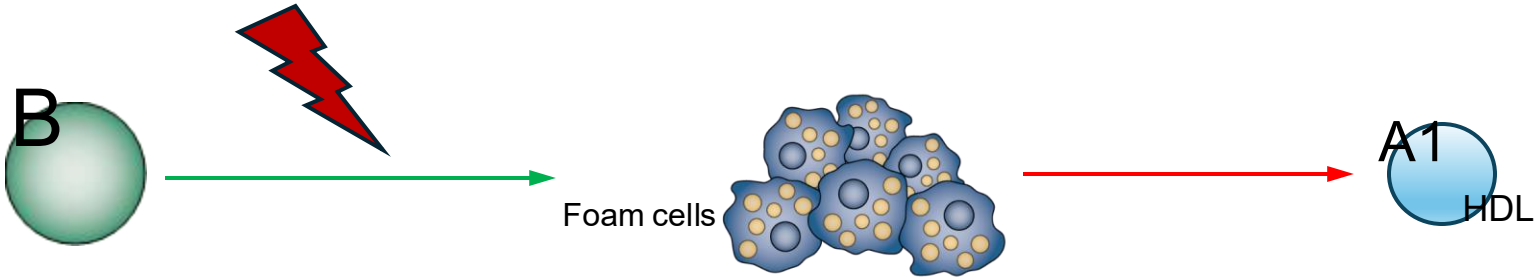
- Lower total **LDL-C** and less **smoking**, but
- More...
  - **HTN** (30→50%)
  - **Prediabetes and DM** (50%)
  - **Obesity** (15→40%)



HTN = hypertension; DM = diabetes mellitus.

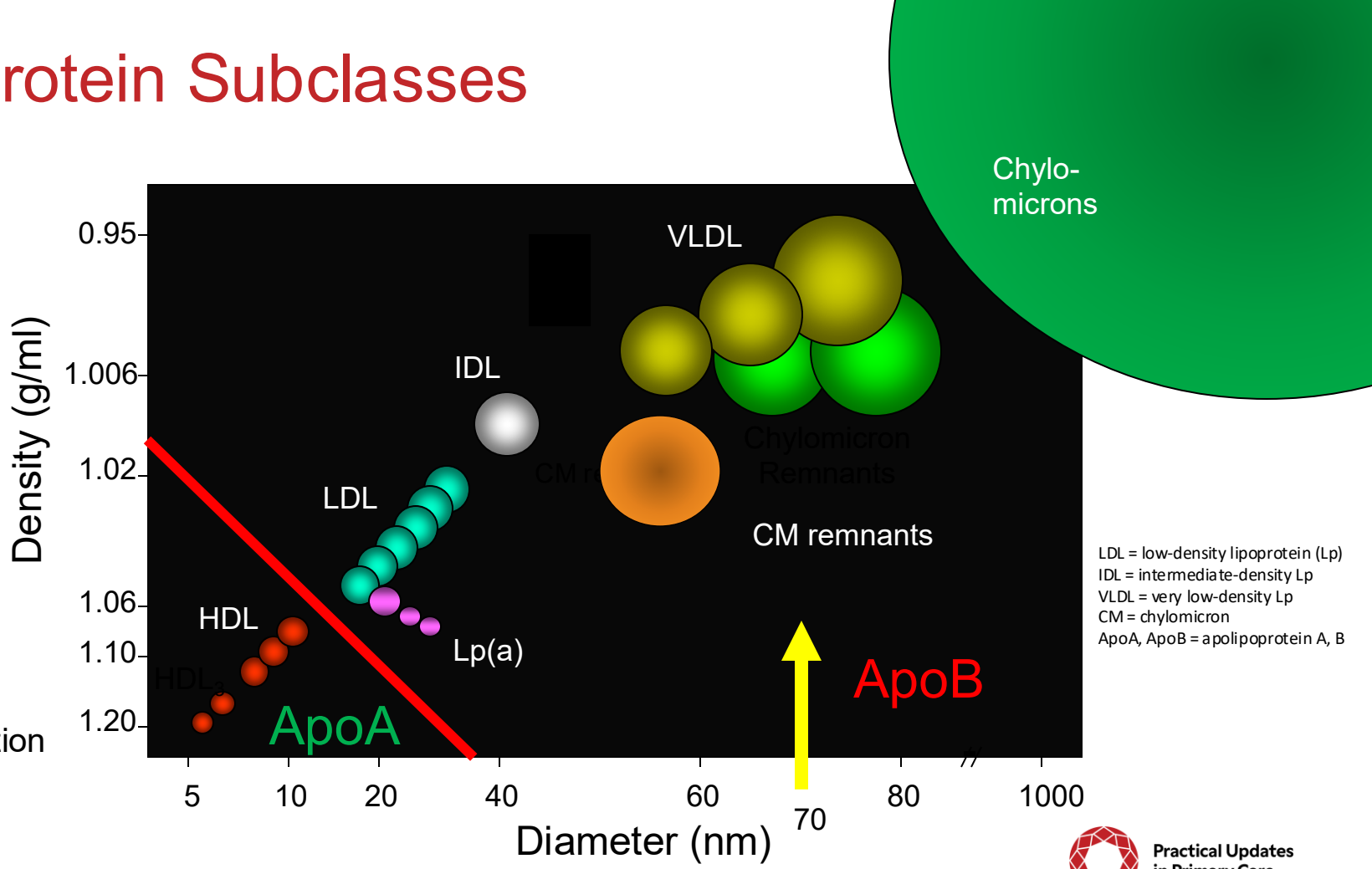
Martin SS, et al. *Circulation*. 2025;151(8):e41-e660.

Response to Retention Hypothesis



HDL = high-density lipoprotein.
Williams KJ, Tabas I. *Curr Opin Lipidol*. 1998;9(5):471-474.

Lipoprotein Subclasses



LDL = low-density lipoprotein (Lp)
IDL = intermediate-density Lp
VLDL = very low-density Lp
CM = chylomicron
ApoA, ApoB = apolipoprotein A, B

Gel Fractionation

Gofman/Berkeley Heart Lab.

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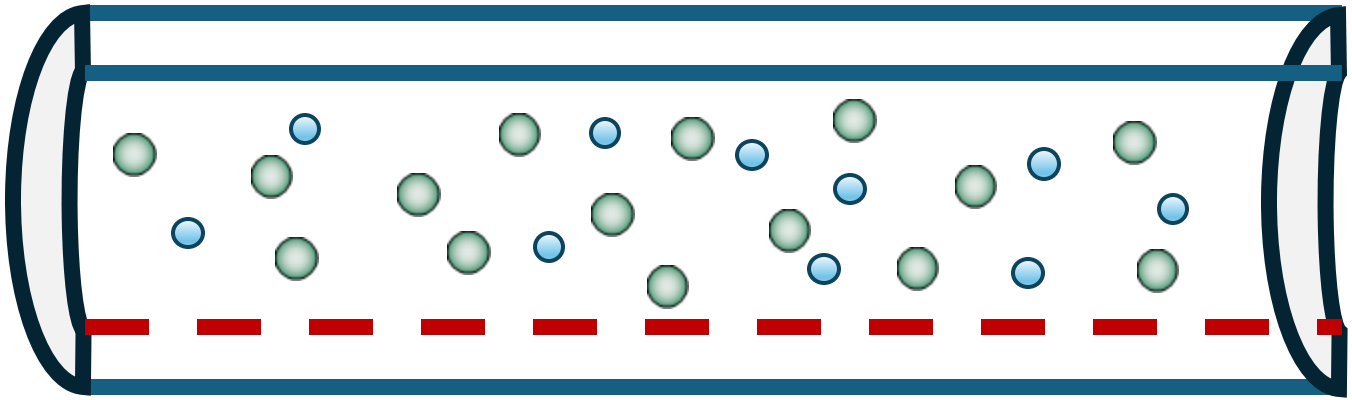
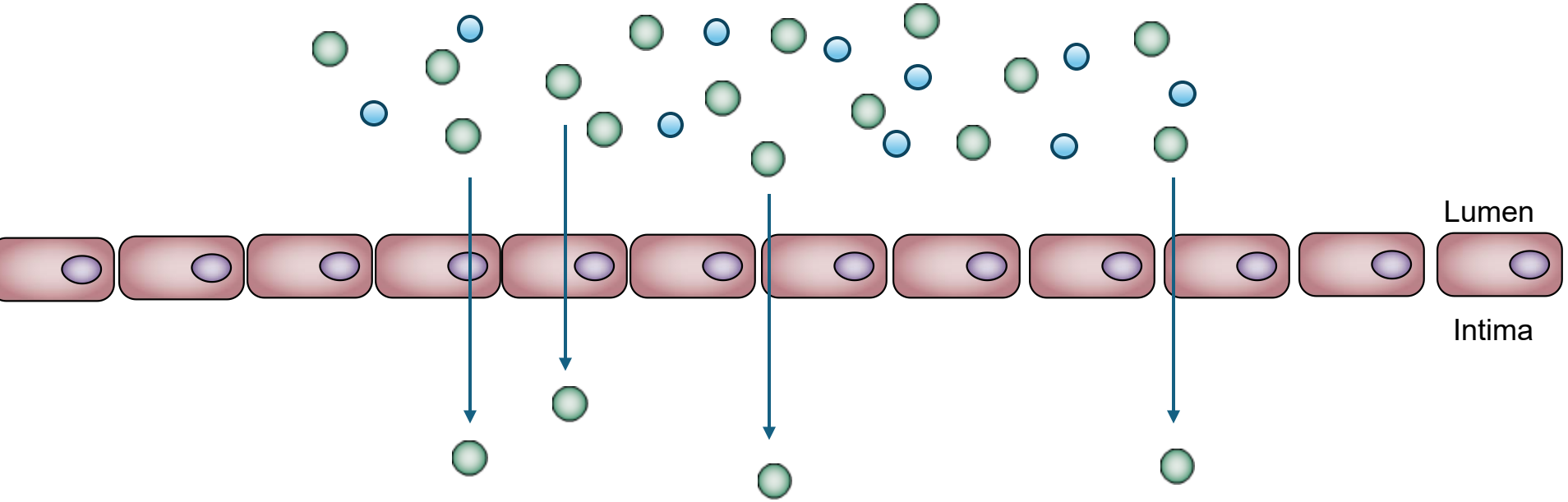
ApoB-Lps

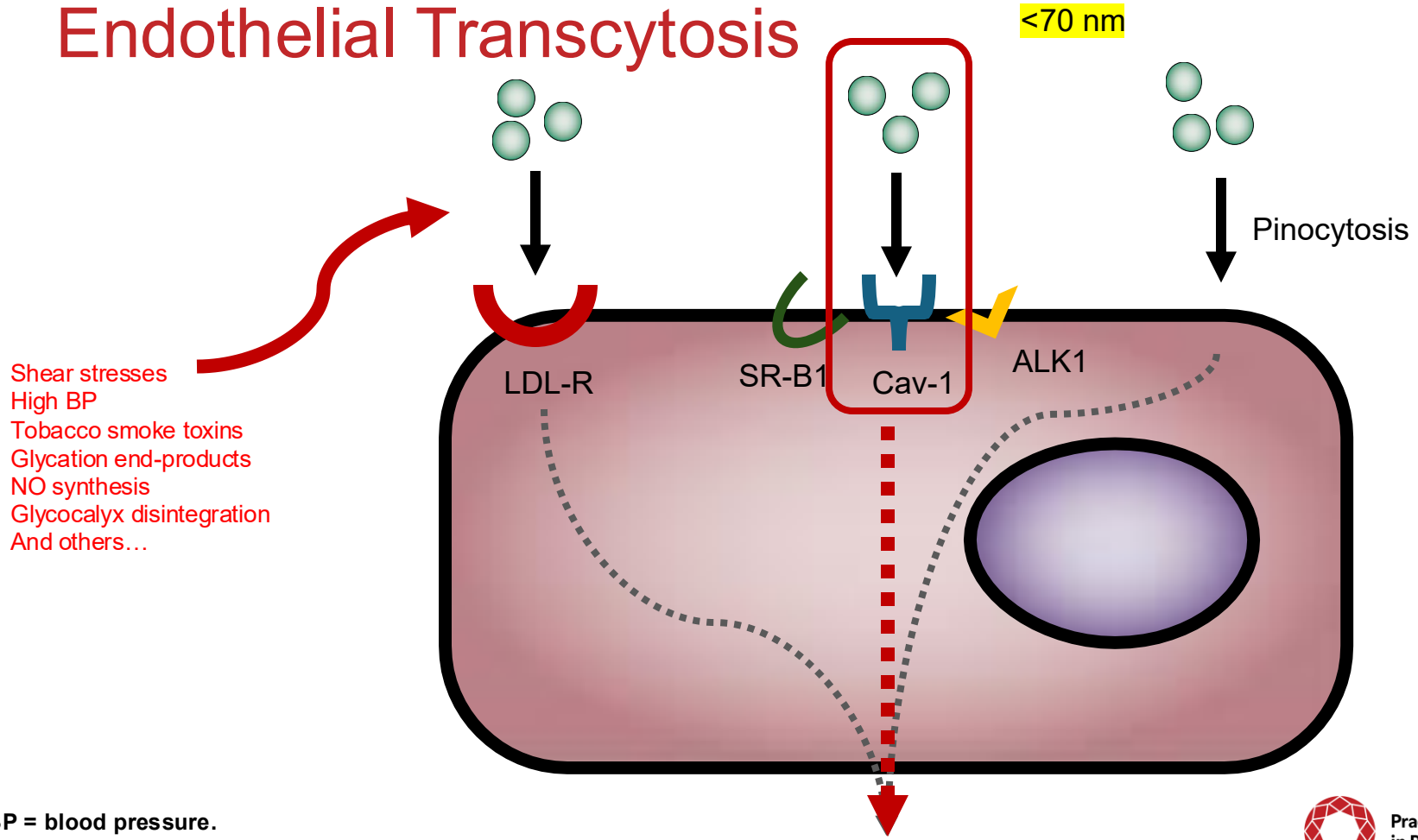
- **LDL**
- Remnants (TG)
- Lp(a)



TG = triglycerides.



Endothelial Transcytosis



BP = blood pressure.

Adapted from Ho TWW, et al. *Curr Atheroscler Rep*. 2023;25(8):457-465.

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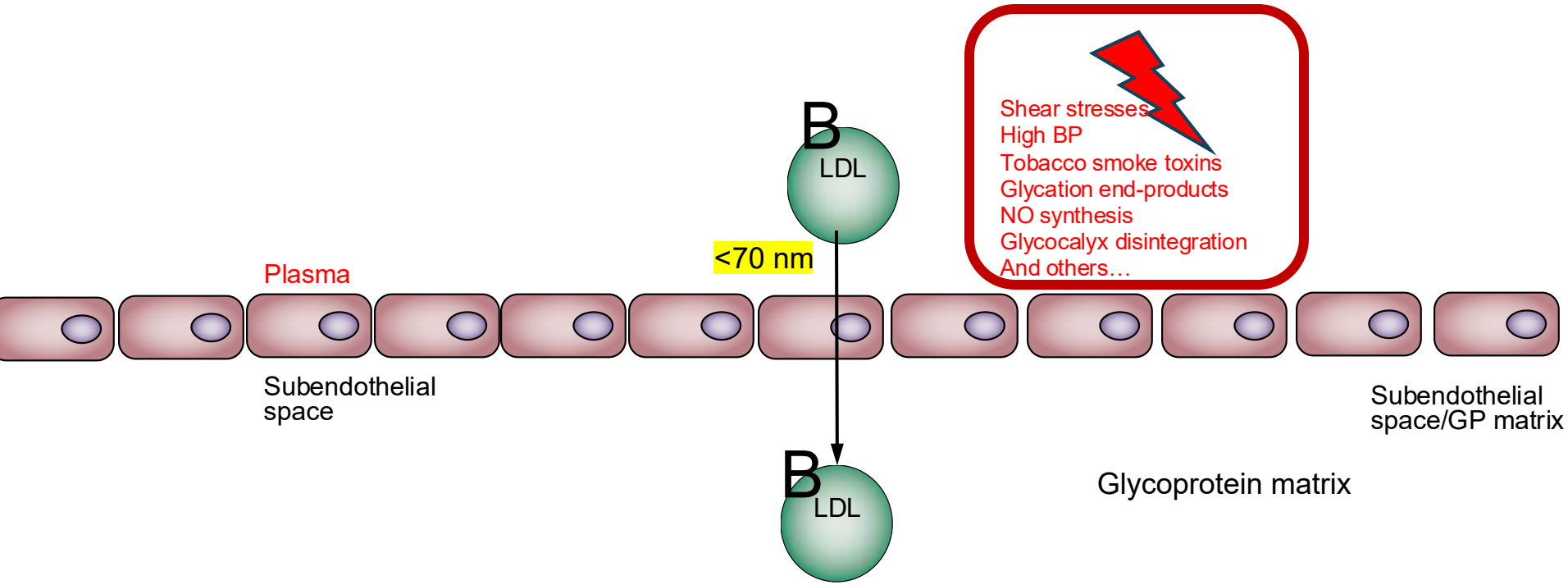
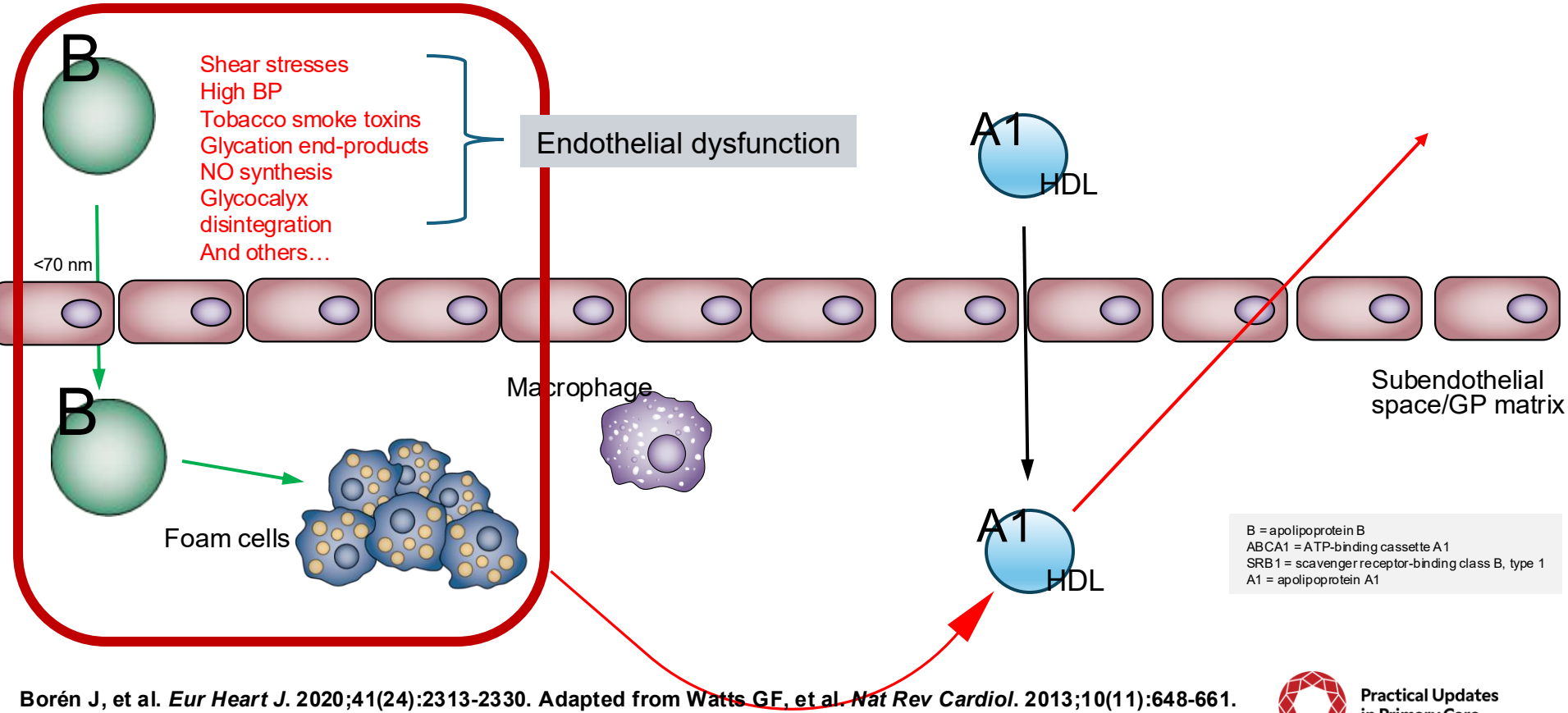
LDL → Atherosclerosis



Plaque Management



Borén J, et al. *Eur Heart J*. 2020;41(24):2313-2330. Adapted from Watts GF, et al. *Nat Rev Cardiol*. 2013;10(11):648-661. Wang L, et al. *J Lipid Res*. 2009;50(2):204-213. Takahashi M, et al. *J Lipid Res*. 2013;54(4):1124-1134.

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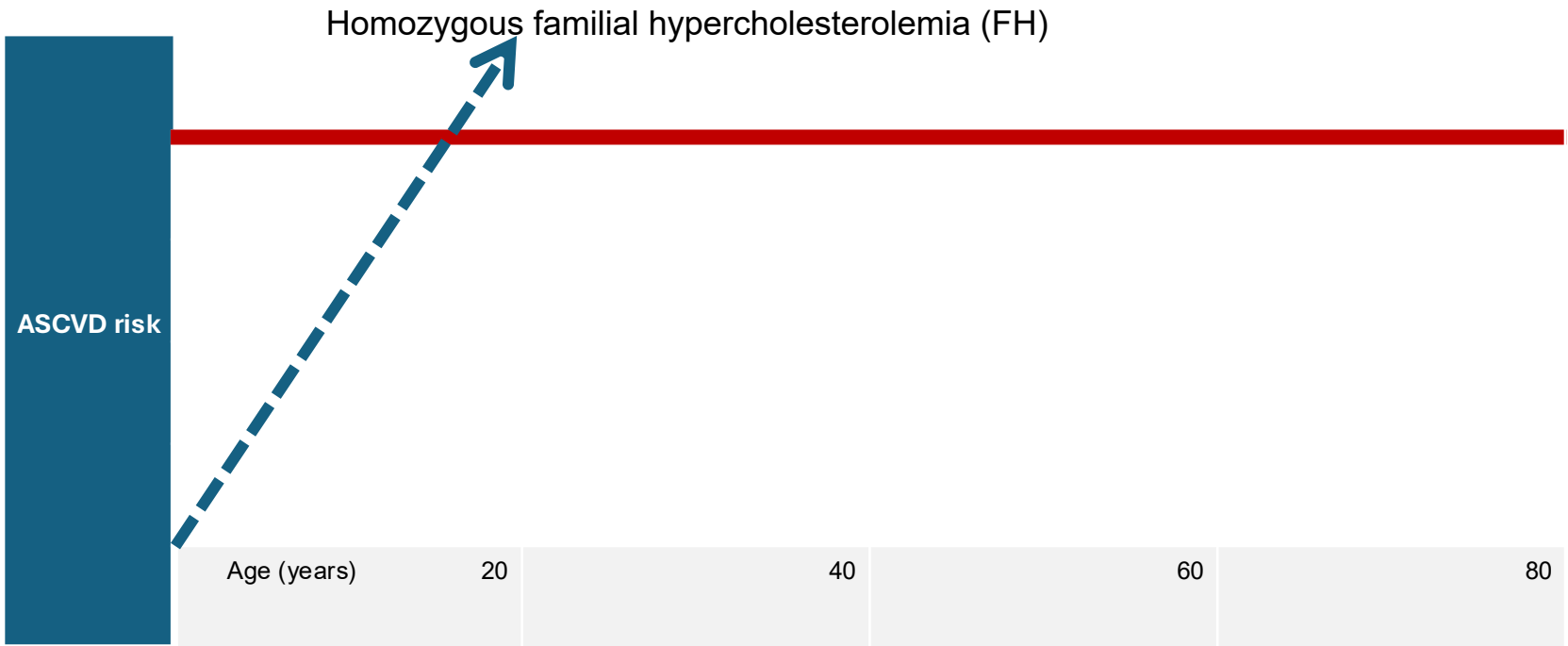
- LDL (and other apoB-Lp) are building blocks for plaque
- Multiple factors enable, accelerate plaque formation
- HDL slows, stops, repairs plaque

Time to Event – (The FH Model)



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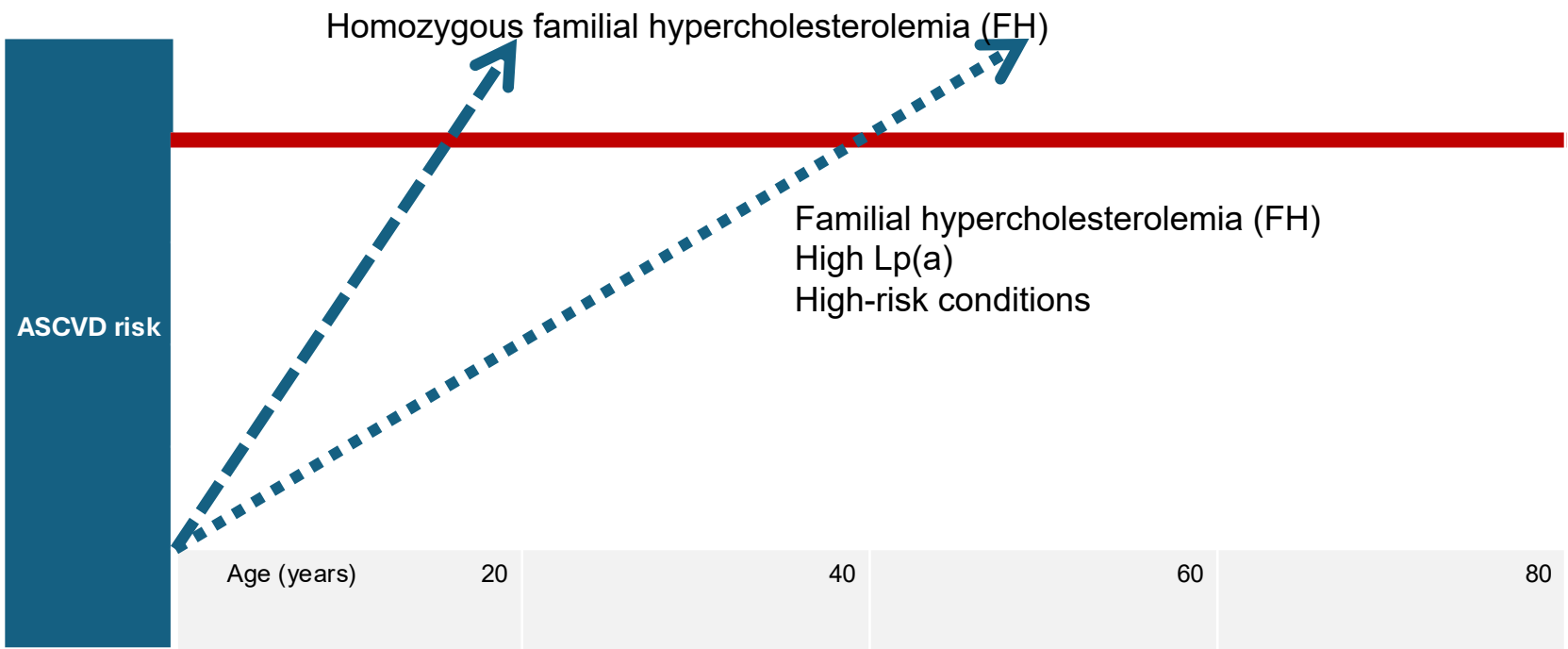
Time to Event – (The FH Model)



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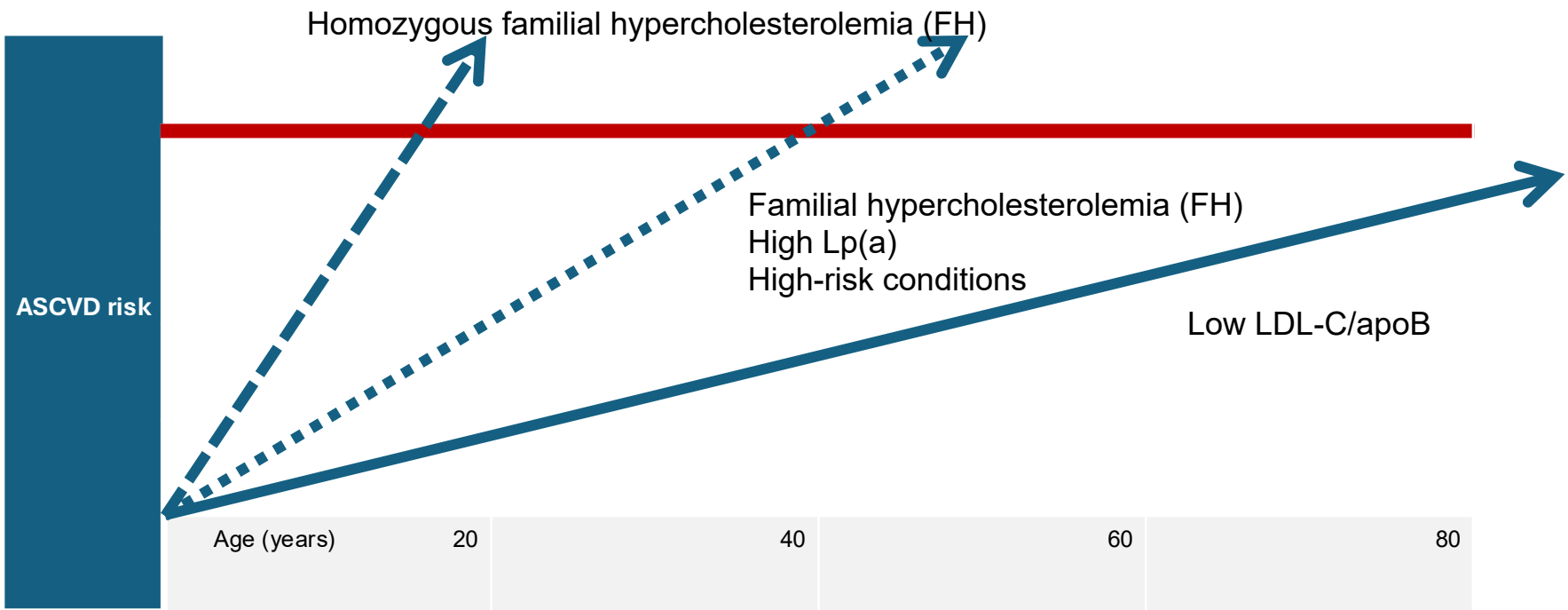
Time to Event – (The FH Model)



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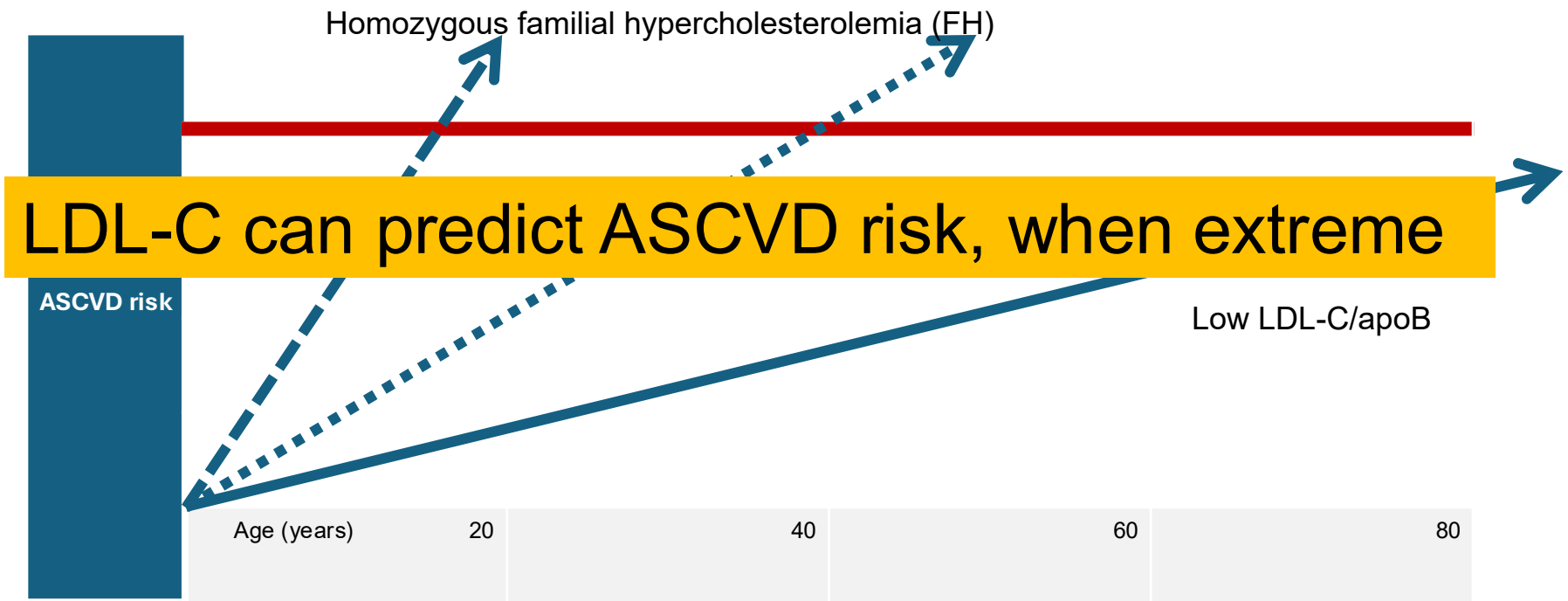
Time to Event – (The FH Model)



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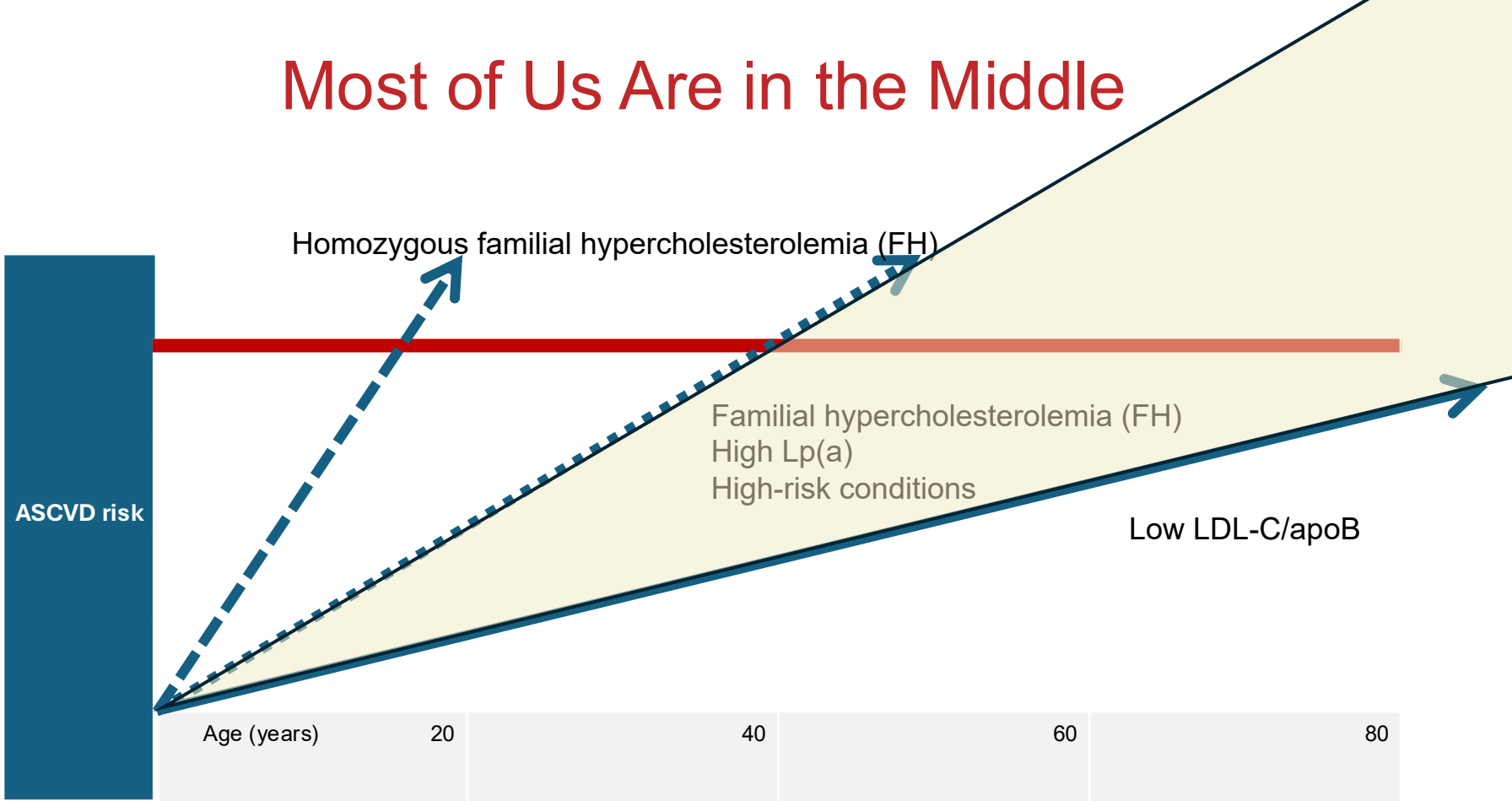
Most of Us Are in the Middle



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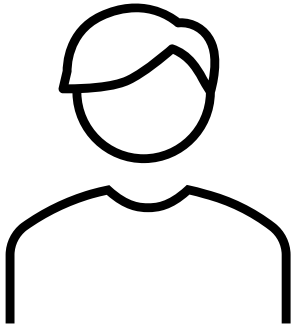
1. Medical history?
2. Features that promote risk?
3. How much plaque?

?????



- ✓Sex:
- ✓Age:
- ✓TC:
- ✓HDL-C:
- ✓SBP:
- ✓BMI:
- ✓EGFR:
- ✓Diab?
- ✓Smoke?
- ✓Rx?
- ✓Zip code?

TC = total cholesterol; SBP = systolic BP; BMI = body mass index; EGFR = estimated glomerular filtration rate.

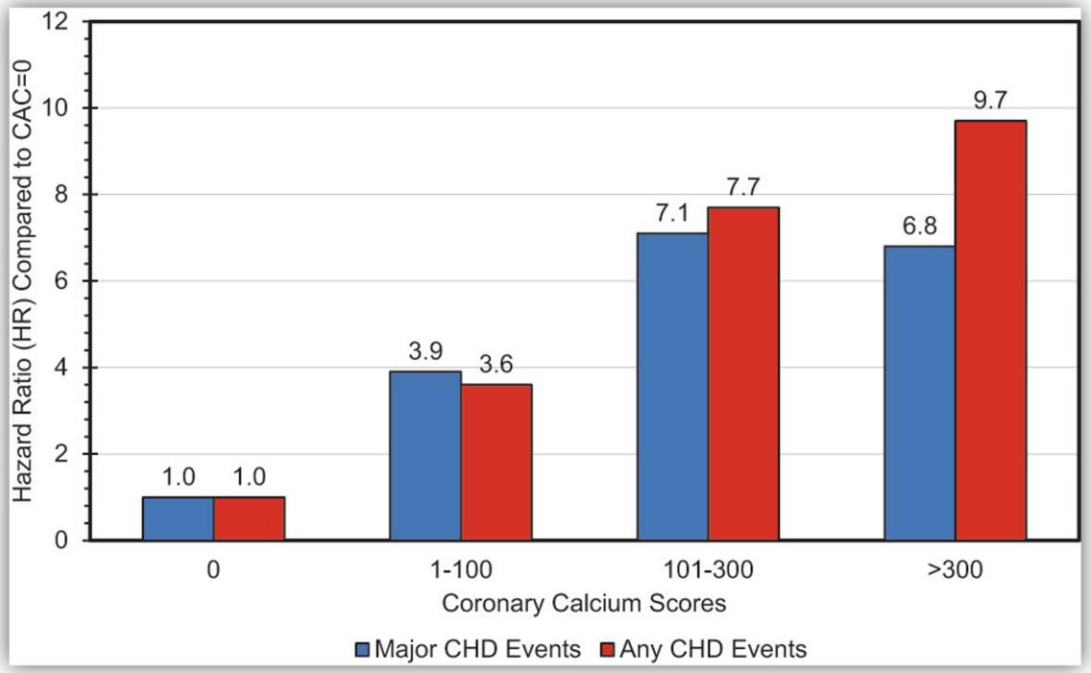
The American Heart Association PREVENT™ Online Calculator. Accessed July 3, 2025. https://professional.heart.org/en/guidelines-and-statements/prevent-calculator.

Other Important Risk Factors

- Inherited risk
- Other lipid disorders (Lp[a], apoB, TRL)
- Reproductive conditions (PCOS, gestational DM, preeclampsia)
- High-risk body morphology (PLD, IR at lower BMI, obesity)
- Autoimmune inflammatory diseases (SLE, RA, psoriasis)
- HIV
- CKD

TRL = triglyceride-rich lipoproteins; PCOS = polycystic ovary syndrome; PLD = partial lipodystrophy; IR = insulin resistance; SLE = systemic lupus erythematosus; RA = rheumatoid arthritis; CKD = chronic kidney disease.

Hazard Ratio for CHD Events per CACS: Ages 45-84 yo, MESA, Median F/U 3.9 Yrs



More plaque
→ more risk

CACS = coronary artery calcium score; CHD = coronary heart disease.
Martin SS, et al. *Circulation*. 2024;149(8):e347-e913.

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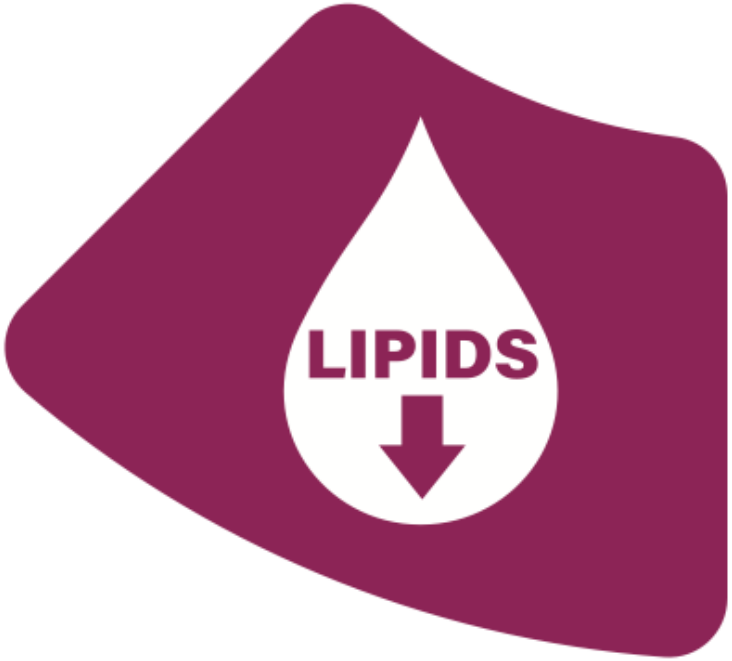
AHA. Accessed July 3, 2025. https://www.heart.org/en/healthy-living/healthy-lifestyle/lifes-essential-8.



AHA. Accessed July 3, 2025. https://www.heart.org/en/healthy-living/healthy-lifestyle/lifes-essential-8.

Medications to Lower LDL-C/ApoB

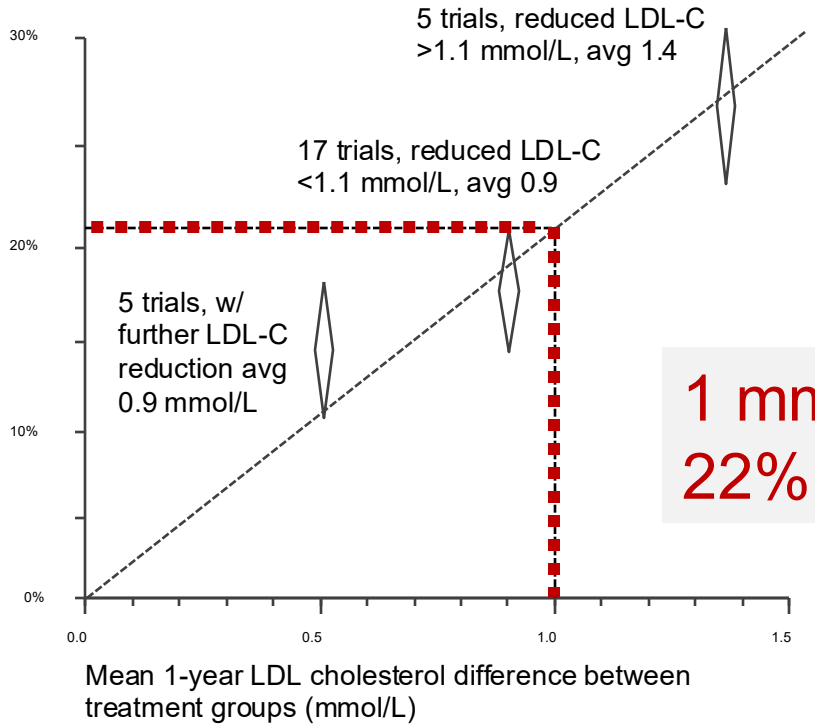
Statins

- **Rosuvastatin**
- **Atorvastatin**
- Simvastatin
- Pravastatin
- Pitavastatin
- Fluvastatin
- Lovastatin

Meta-Analysis of 26 Different RCTs

Proportional reduction in events

- RCTs >2 yrs, >1000 participants
- 26 studies
- >170K participants
- Major CVE outcomes



1 mmol/L reduction → 22% event reduction

RCTs = randomized controlled trials; CVE = CV event.
Baigent C, et al. *Lancet*. 2010;376(9753):1670-1681.

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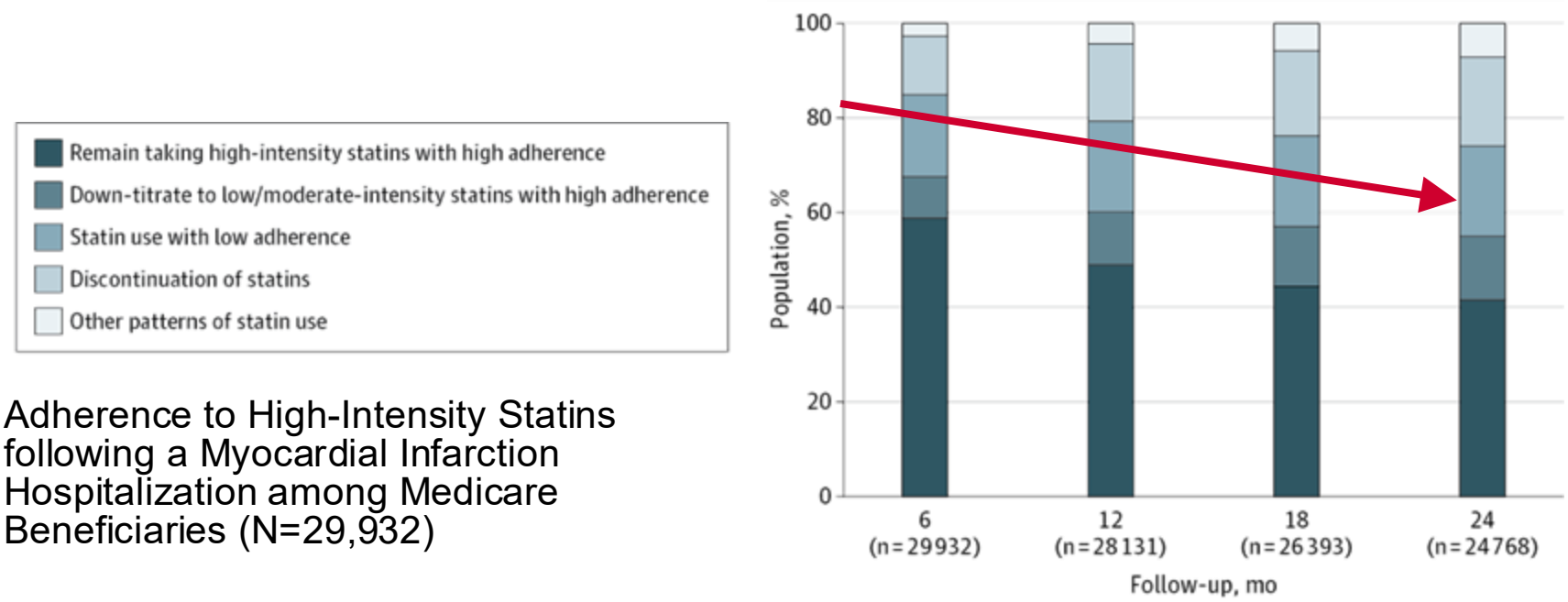
Pattern of Statin Use after Discharge for Myocardial Infarction among Medicare Beneficiaries 66-75 Years of Age



Adherence to High-Intensity Statins following a Myocardial Infarction Hospitalization among Medicare Beneficiaries (N=29,932)

Colantonio LD, et al. *JAMA Cardiol*. 2017;2(8):890-895.

Medications to Lower LDL-C/ApoB

Statins

- Rosuvastatin
- Atorvastatin
- Simvastatin
- Pravastatin
- Pitavastatin
- Fluvastatin
- Lovastatin

Non-statins

- **Ezetimibe**
- **PCSK9 inhibitors**
- **Bempedoic acid**
- **Bile acid sequestrants**
- **Inclisiran**

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Section 2: Management of LDL-C for Primary and Secondary ASCVD Prevention

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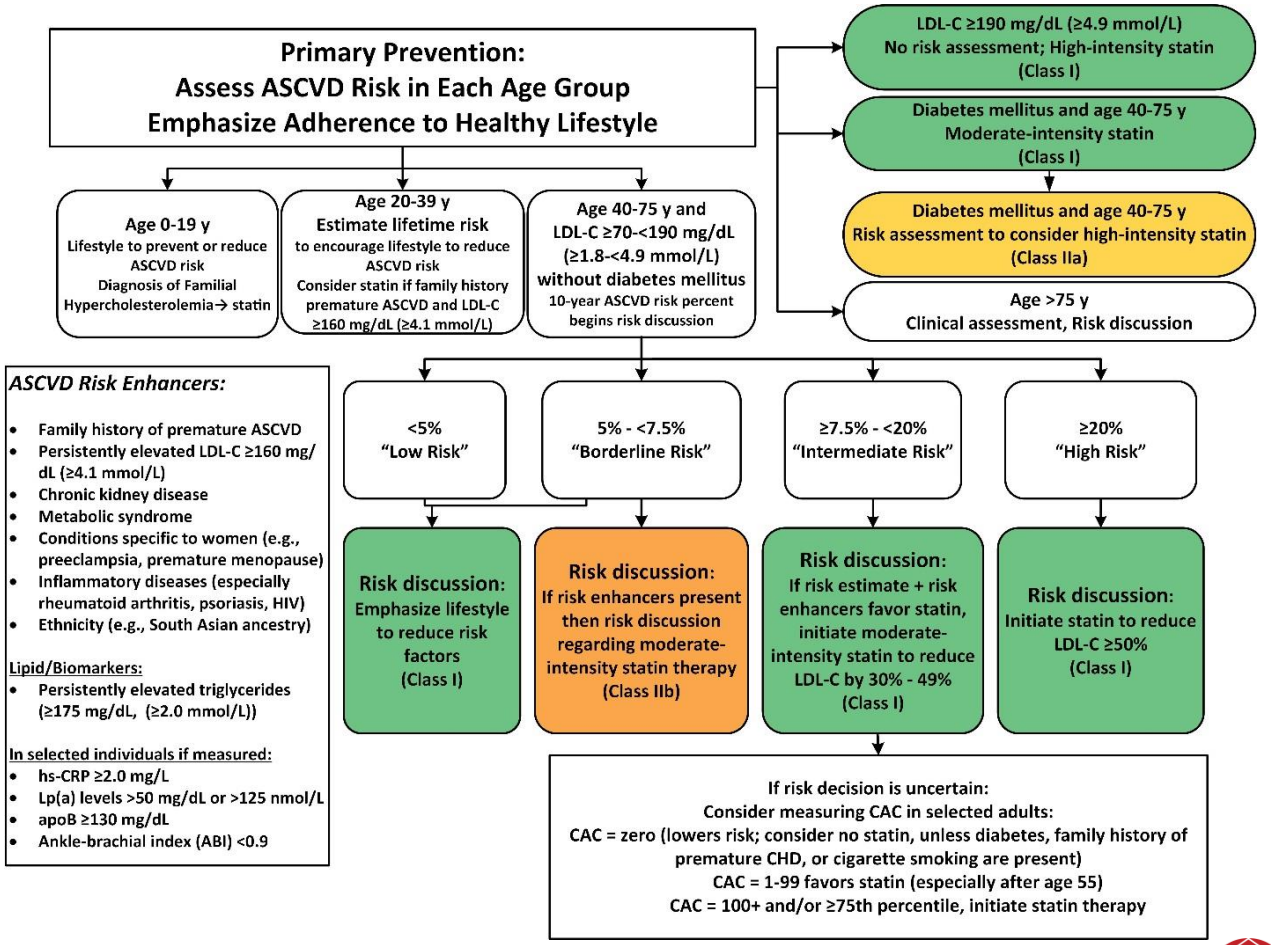
Director, Advanced Lipid Disorders Clinic, Division of Cardiology
Director, Digital Health Innovations Lab, Division of Cardiology
Faculty Leader, Barker Firm, Osler Internal Medicine Residency
Core Faculty, Ciccarone Center for the Prevention of CVD



Grundy SM, et al. *Circulation*. 2019;139(25):e1082-e1143.

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Guideline Recommendations for Severe Hypercholesterolemia (LDL-C ≥190 mg/dL)

COR	LOE	Recommendations
I	B-R	If 20-75 y/o with LDL-C ≥190* → maximally tolerated statin recommended
IIa	B-R	If 20-75 y/o with LDL-C ≥190 who achieve <50% LDL-C drop on maximally tolerated statin and/or LDL-C level of ≥100, ezetimibe reasonable
IIb	B-R	If 30-75 y/o with heterozygous FH & LDL-C ≥100 on maximally tolerated statin + ezetimibe, consider PCSK9i

COR = class of recommendation; LOE = level of evidence.
Grundy SM, et al. *Circulation*. 2019;139(25):e1082-e1143.

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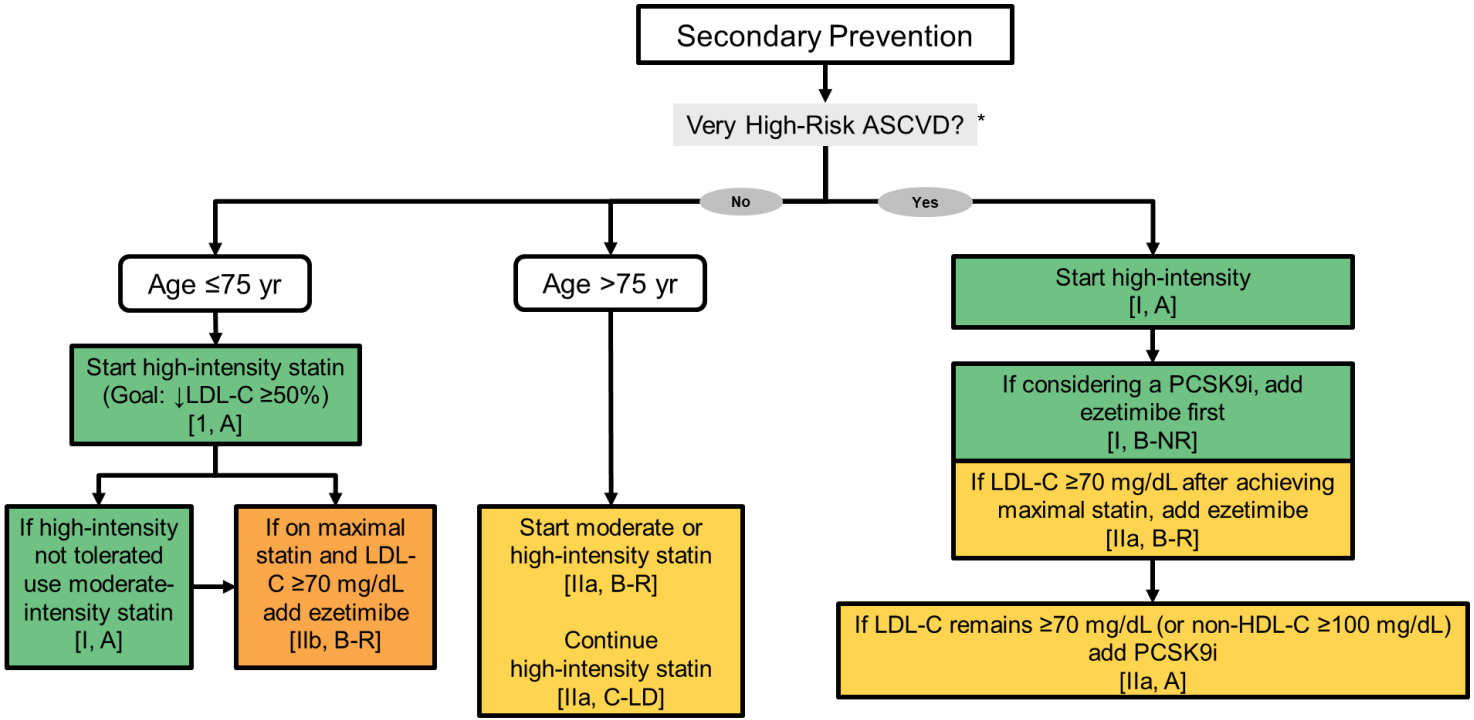
2018 AHA/ACC Cholesterol Guideline



***Very high-risk = multiple major ASCVD events or 1 ASCVD event with multiple additional high-risk conditions.**
AHA = American Heart Association; ACC = American College of Cardiology.
Grundy SM, et al. *Circulation*. 2019;139(25):e1082-e1143.

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2022 ACC Non-Statin Consensus Pathway

OPTIONAL INTERVENTIONS TO CONSIDER IN APPROPRIATE PATIENT GROUPS:

- Referral to a lipid specialist and registered dietitian/registered dietitian nutritionist
- Ezetimibe
- Bile acid sequestrants
- PCSK9 mAbs
- Bempedoic acid
- Inclisiran
- LDL apheresis may be considered by lipid specialist for patients with familial hypercholesterolemia
- Lomitapide (only in HoFH)
- Evinacumab (only in HoFH)

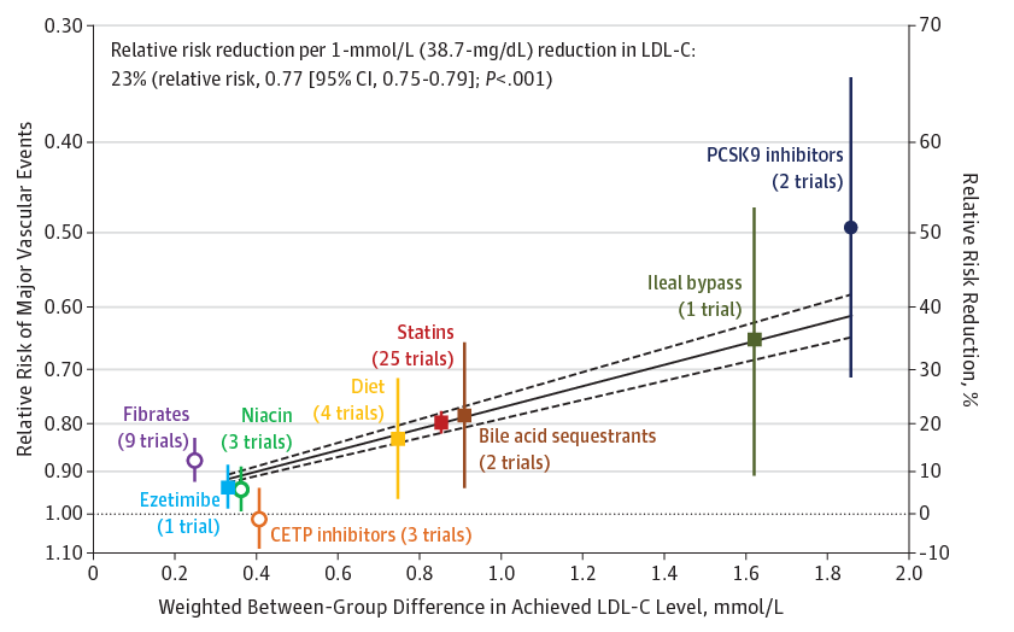
Key Takeaways

- LDL-C 55 mg/dL threshold for "very high risk"
- LDL-C 70 mg/dL threshold for "high risk"
- >25% further LDL-C reduction, can use a PCSK9i next after statin therapy

HoFH = homozygous FH.

Lloyd-Jones DM, et al. *J Am Coll Cardiol*. 2022;80(14):1366-1418.

Association between LDL-C Lowering and CV Risk Reduction among Different Therapeutic Interventions



Silverman MG, et al. *JAMA*. 2016;316(12):1289-1297.

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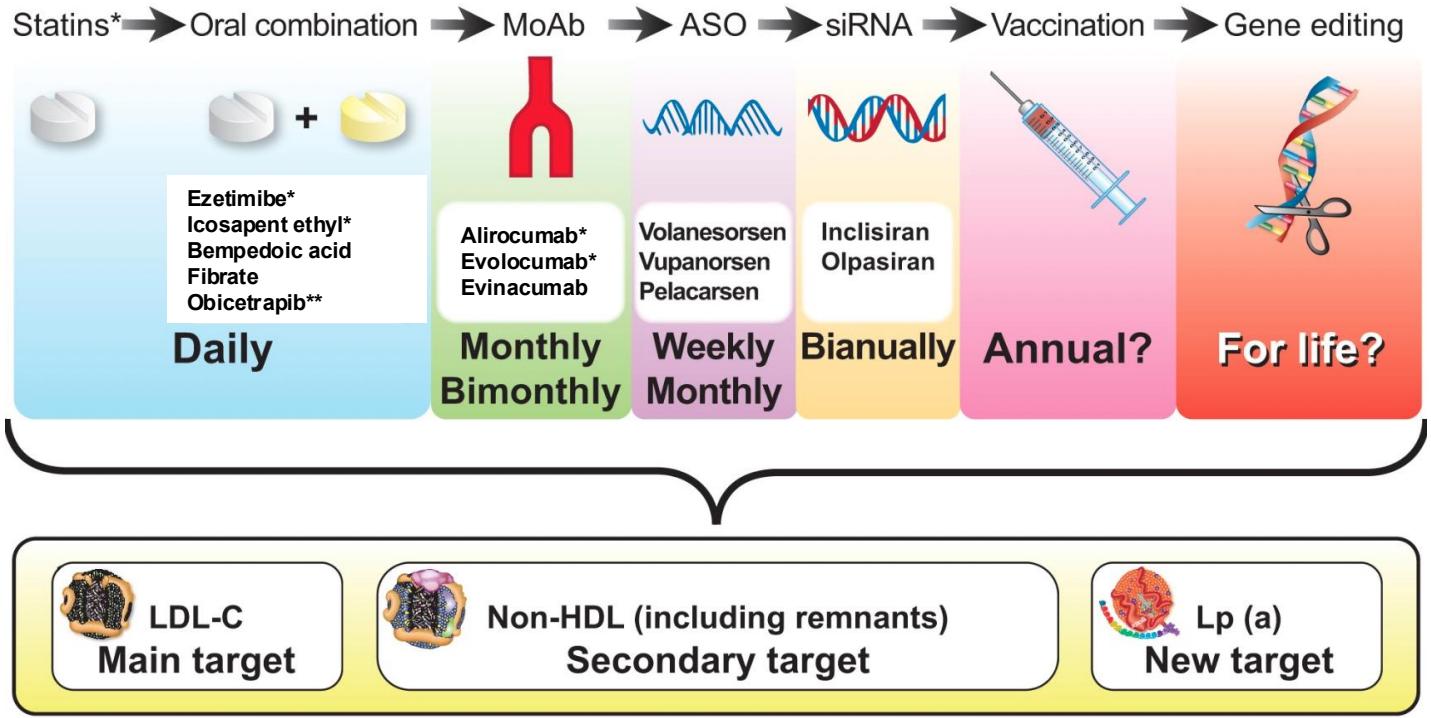
Evolution of Lipid-Lowering Therapies



*Therapies shown to decrease CV events; **Obicetrapib is currently investigational.
MoAb = monoclonal antibody; ASO = antisense oligonucleotide.
Tokgözoğlu L, et al. *Eur Heart J*. 2022;43(34):3198-3208.

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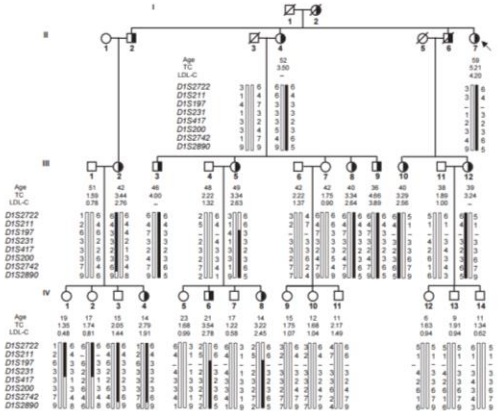
Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

Marianne Abifadel[1,2], Mathilde Varret[1], Jean-Pierre Rabès[1,3], Delphine Allard[1], Khadija Ouguerram[4], Martine Devillers[1], Corinne Cruaud[5], Suzanne Benjannet[6], Louise Wickham[6], Danièle Erlich[1], Aurélie Derré[1], Ludovic Villéger[1], Michel Farnier[7], Isabel Beucler[8], Eric Bruckert[9], Jean Chambaz[10], Bernard Chanu[11], Jean-Michel Lecerf[12], Gerald Luc[12], Philippe Moulin[13], Jean Weissenbach[5], Annick Prat[6], Michel Krempf[4], Claudine Junien[1,3], Nabil G Seidah[6] & Catherine Boileau[1,3]

Autosomal dominant hypercholesterolemia (ADH; OMIM144400), a risk factor for coronary heart disease, is characterized by an increase in low-density lipoprotein cholesterol levels that is associated with mutations in the genes *LDLR* (encoding low-density lipoprotein receptor) or *APOB* (encoding apolipoprotein B). We mapped a third locus associated with ADH, *HCHOLA3* at 1p32, and now report two mutations in the gene *PCSK9* (encoding proprotein convertase subtilisin/kexin type 9) that cause ADH. *PCSK9* encodes NARC-1 (neural apoptosis regulated convertase), a newly identified human subtilase that is highly expressed in the liver and contributes to cholesterol homeostasis.

Pedigree in French family with xanthomas, premature CVD, and PCSK9 mutation

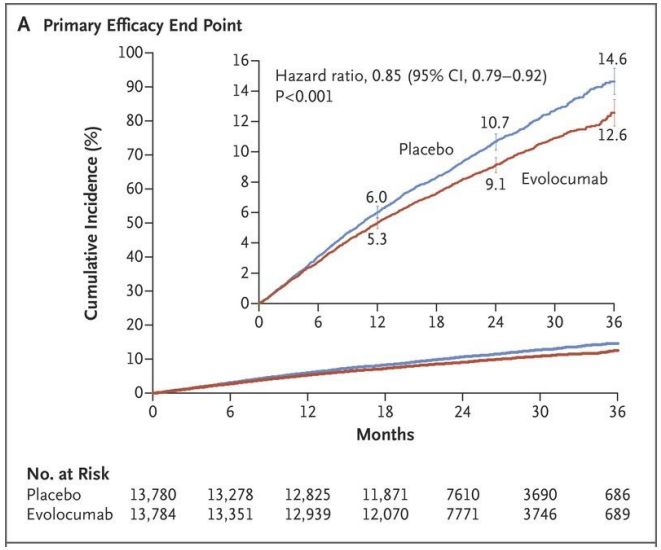


Abifadel M, et al. *Nat Genet*. 2003;34(2):154-156.

Major Trial Evidence for PCSK9i

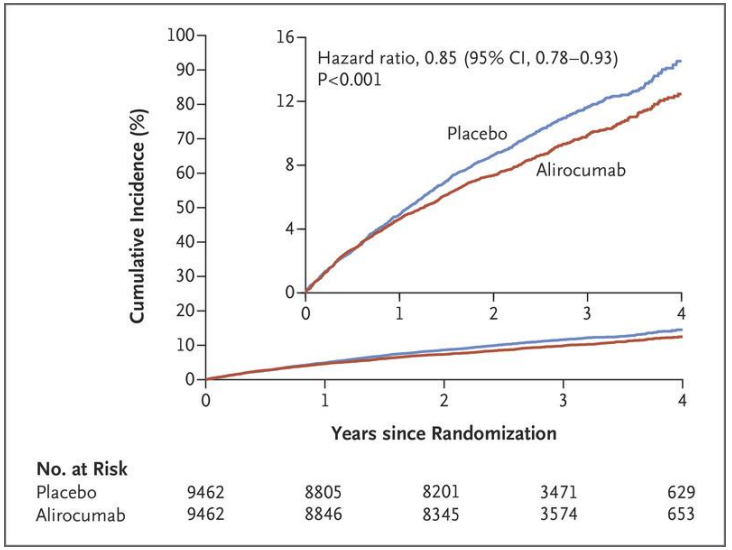
FOURIER

27,564 pts w/ ASCVD
Median 2.2 yrs
LDL-C 92 → 30



ODYSSEY Outcomes

18,924 pts w/ ACS
Median 2.8 yrs
LDL-C 92 → 30 → 48 → 66



ACS = acute coronary syndrome.

Sabatine MS, et al. *N Engl J Med*. 2017;376(18):1713-1722. Schwartz GG, et al. *N Engl J Med*. 2018;379(22):2097-2107.

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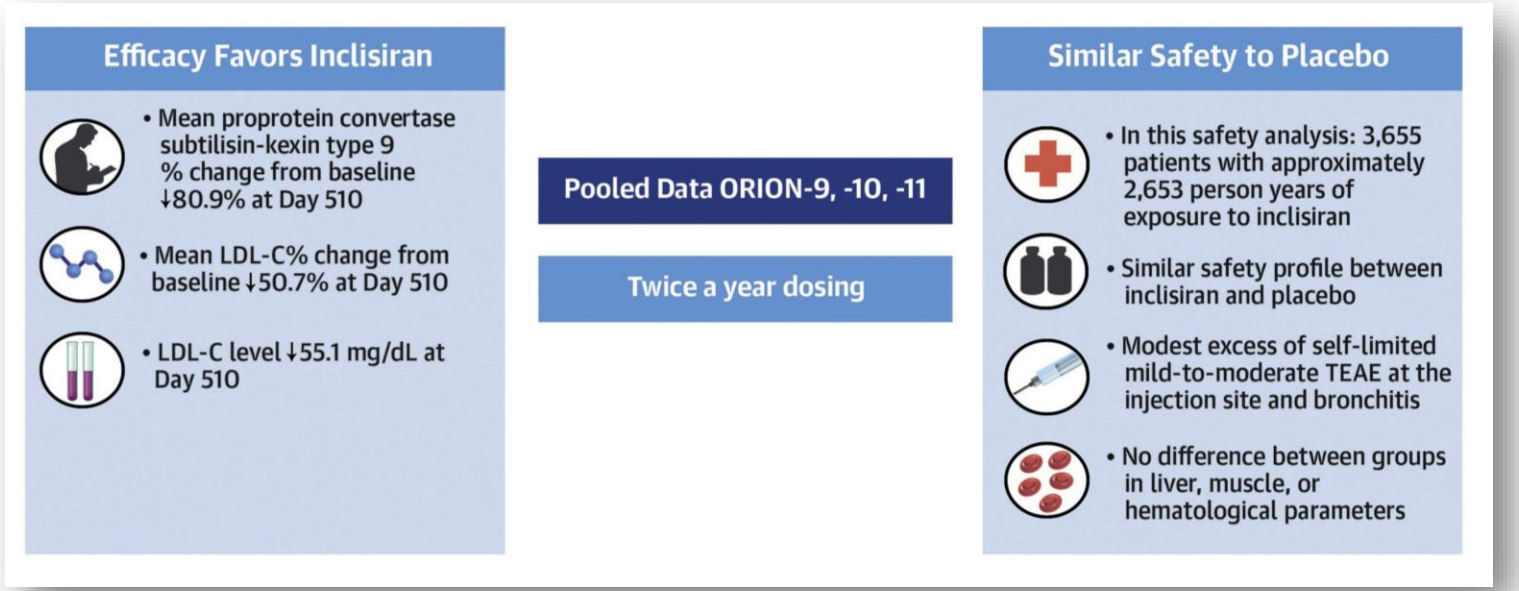
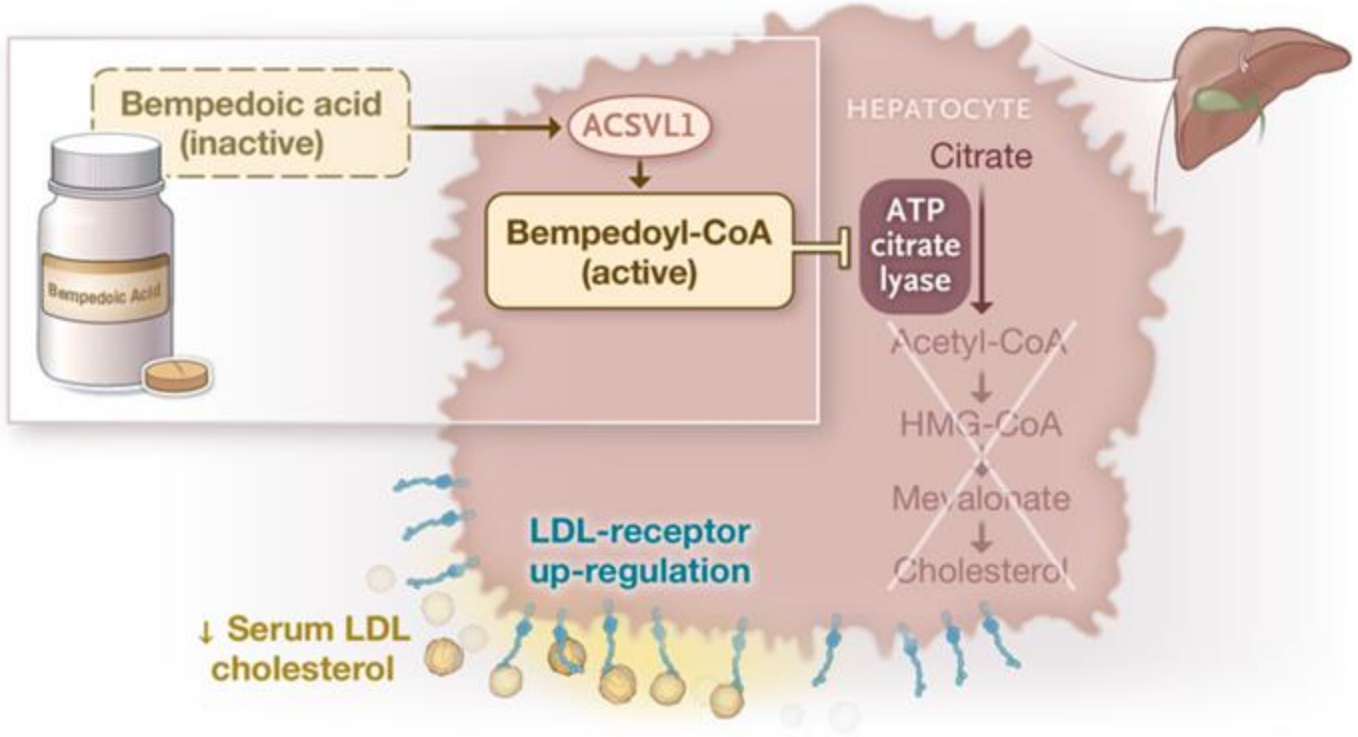
Inclisiran Safety and Efficacy



TEAE = treatment-emergent adverse event.

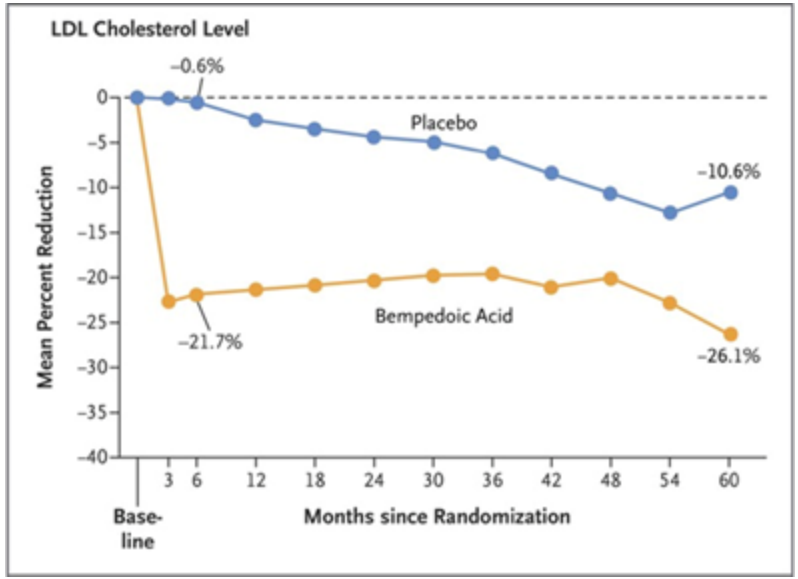
Wright RS, et al. *J Am Coll Cardiol*. 2021;77(9):1182-1193.

Bempedoic Acid: Mechanism of Action



Nissen SE, et al. *N Engl J Med*. 2023;388(15):1353-1364.

CLEAR Outcomes Trial of Bempedoic Acid



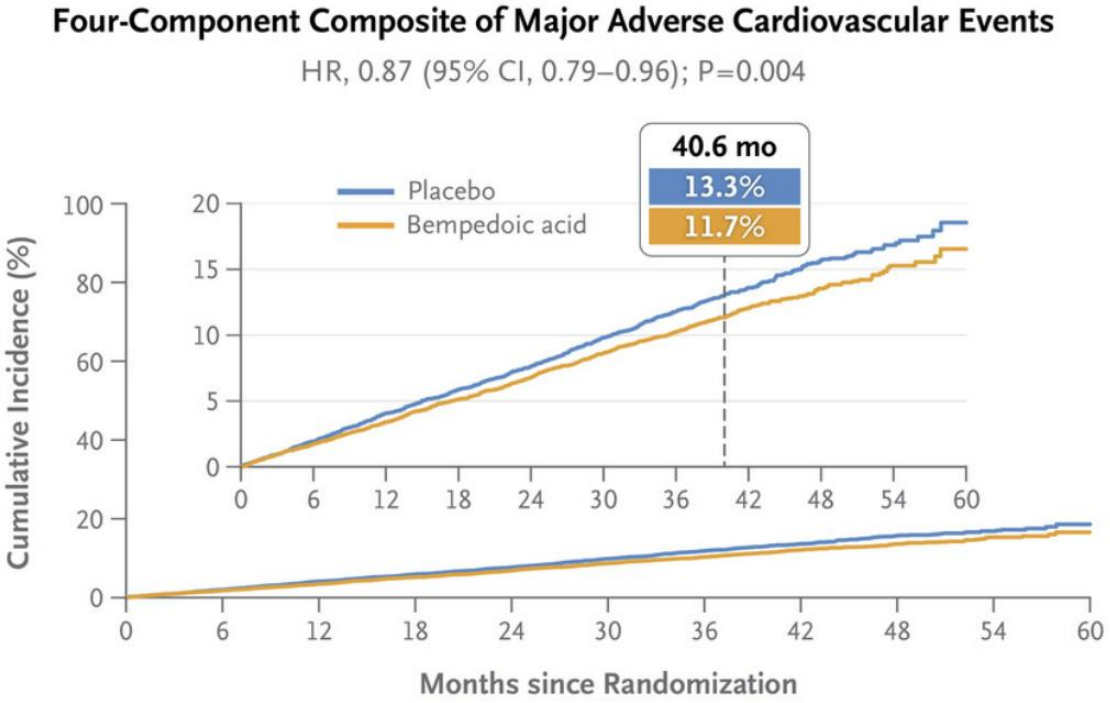
- Double-blind randomized trial of 13,970 statin-intolerant patients with LDL-C 100 mg/dL or greater in 1^0 and 2^0 prevention

Bempedoic acid 180 mg daily	Placebo

- 40.6 months median follow-up, bempedoic acid vs placebo resulted in reduction of LDL-C by 21.7%
- Small increases in the incidence of gout and cholelithiasis

Nissen SE, et al. *N Engl J Med*. 2023;388(15):1353-1364.

CLEAR Outcomes: CV Event Reduction



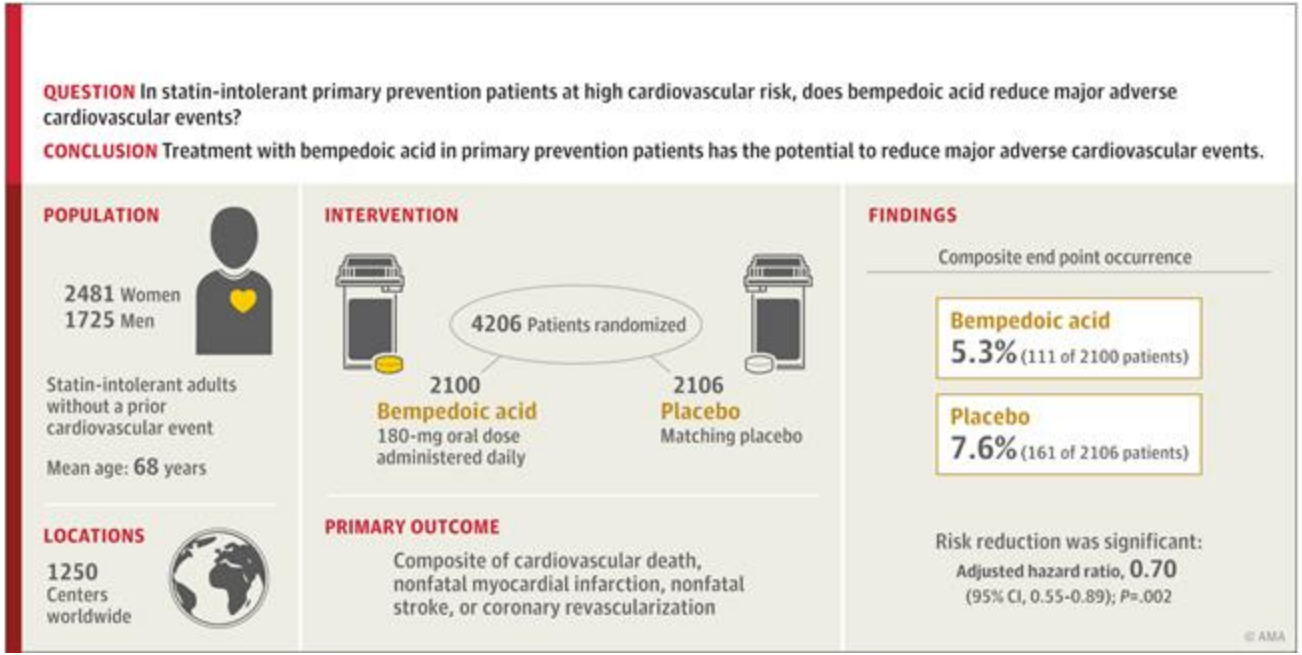
- Primary end-point 4-component MACE was reduced by 13%
- Secondary 3-component MACE 15%, myocardial infarction 23%, and coronary revascularization 19%

HR = hazard ratio; CI = confidence interval; MACE = major adverse cardiovascular event.

Nissen SE, et al. *N Engl J Med*. 2023;388(15):1353-1364.

Practical Updates in Primary Care

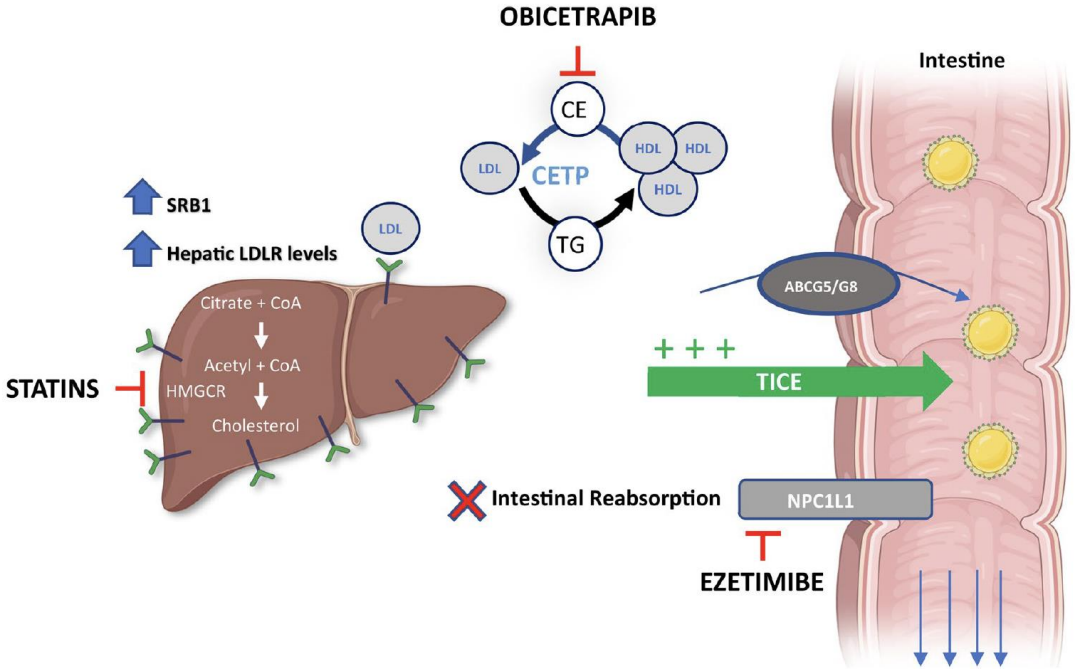
CLEAR Outcomes – Primary Prevention



Nissen SE, et al. *JAMA*. 2023;330(2):131-140.

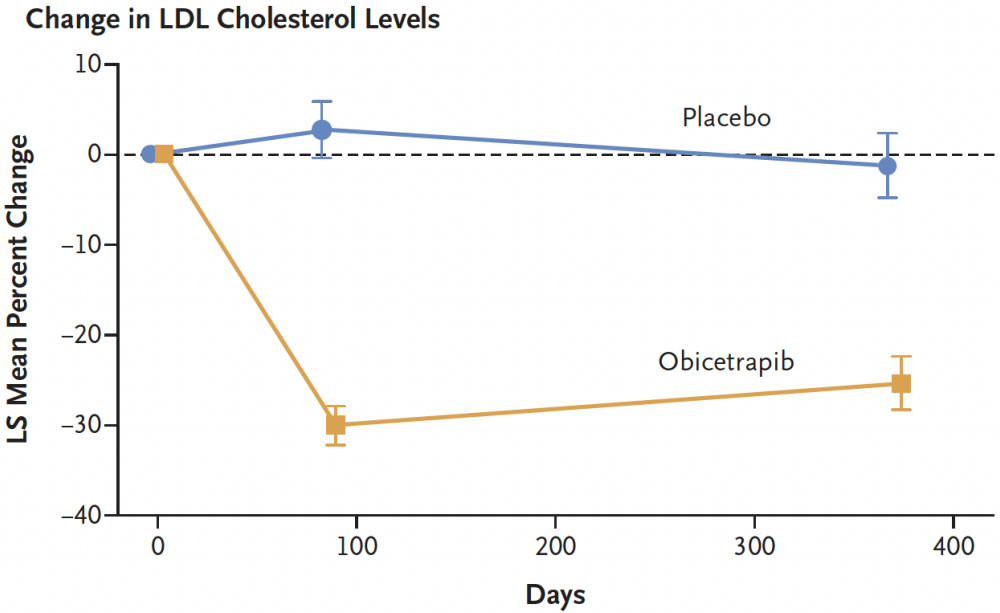
Practical Updates in Primary Care

Obicetrapib: Mechanism of Action



Kastelein JJP, et al. *Curr Atheroscler Rep*. 2024;26(2):35-44.

Obicetrapib among Pts with ASCVD or HeFH on Max LLT: BROADWAY Trial

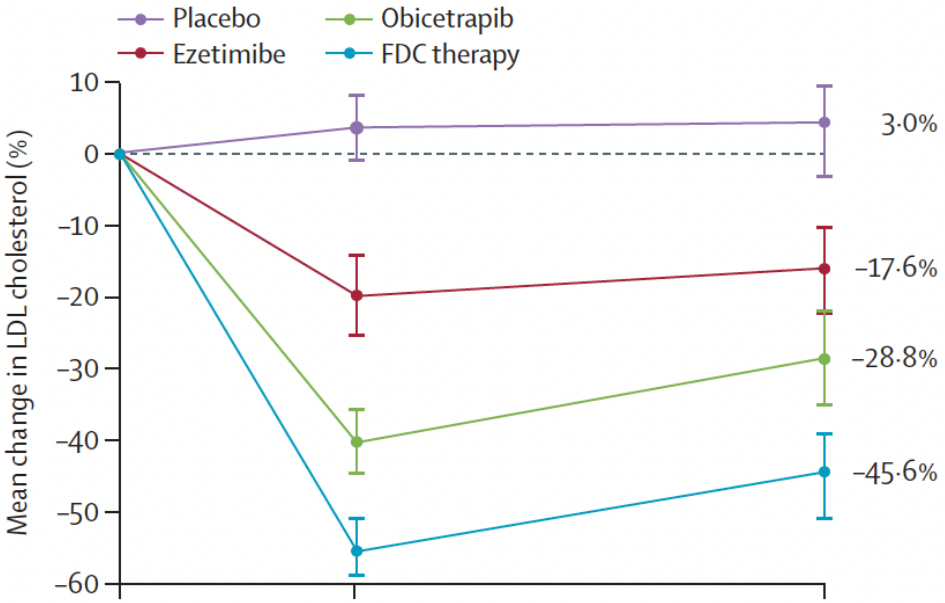


- Obicetrapib led to a 35% reduction in LDL-C (vs 2% for placebo) at day 84
- Incidence of adverse events appeared similar in the 2 groups

HeFH = heterozygous FH; LLT = lipid-lowering therapy; LS = least squares.

Nicholls SJ, et al. *N Engl J Med*. 2025;393(1):51-61.

Fixed-Dose Combination of Obicetrapib and Ezetimibe for LDL-C Reduction: TANDEM Trial



FDC = fixed-dose combination.

Sarraju A, et al. *Lancet*. 2025;405(10491):1757-1768.

Key Learning Points

- Current guidelines recommend targeting LDL-C lowering to reduce ASCVD risk

- Intensity of therapy matched to risk – cardiovascular risk is related to long-term cumulative exposure to LDL/ApoB
  - Lower LDL-C for longer is better

- Primary prevention LDL-C goal of <100 and secondary prevention goal of <70 and ideally <55, especially if very high risk

- On top of a foundation of a healthy lifestyle, statins, and ezetimibe, we have an expanding set of non-statin lipid therapies
  - PCSK9 inhibitors (injectable therapy) have been a game-changer
  - Newer oral option: Bempedoic acid
  - Emerging oral option: Obicetrapib (CETP inhibitor)

Practical Updates in Primary Care

Section 3: Decision-Making for Lipid-Lowering Therapy

Seth S. Martin, MD, MHS, FACC, FAHA, FASPC

Professor, Division of Cardiology, Johns Hopkins School of Medicine
Director, Advanced Lipid Disorders Clinic, Division of Cardiology
Director, Digital Health Innovations Lab, Division of Cardiology
Faculty Leader, Barker Firm, Osler Internal Medicine Residency
Core Faculty, Ciccarone Center for the Prevention of CVD

Case: T.A.

History

- 48-year-old woman s/p hospitalization for NSTEMI → CABG
- MI s/p single-vessel PCI 5 years ago

Risk factor profile

- Hypercholesterolemia
- Family history of early CAD/AMI/SCD

Family history

- Father, brother, P-uncle – AMI ~50 yo (brother SCD)

Physical exam

- Notable for bilateral corneal arcus and thickened Achilles tendons

NSTEMI = non-ST-segment elevation MI; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; MI = myocardial infarction; CAD = coronary artery disease; AMI = acute MI; SCD = sudden cardiac death.

Case: T.A.

- 48 yo woman s/p CABG
- Familial hypercholesterolemia

	TC	TG	HDL-C	LDL-C
Untreated	368	90	43	**304**
Cardiac rehab; atorvastatin 80 mg, ezetimibe 10 mg				**127**
Lipid clinic; PCSK9i added				**46**

AHA/ACC Guidelines: Tailoring Treatment by Risk in Secondary Prevention

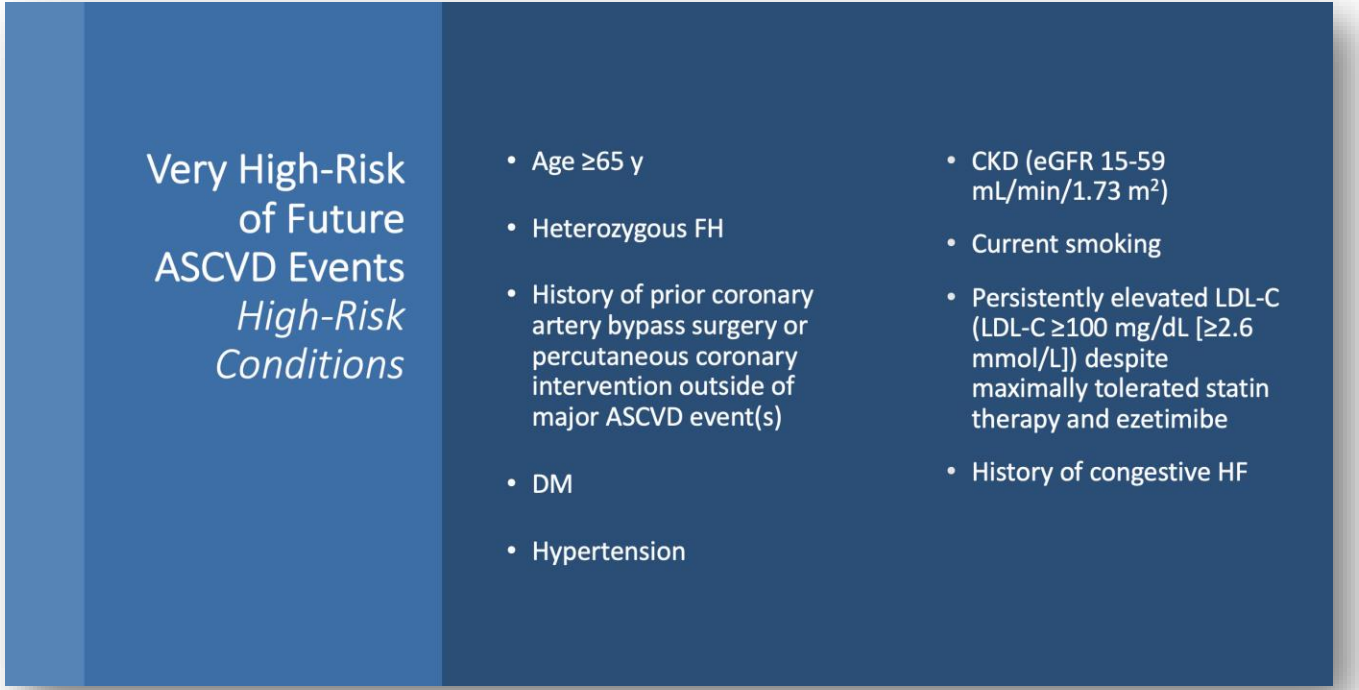
Very High-Risk of Future ASCVD Events *Major ASCVD Events*

- Recent ACS (within the past 12 months)
- History of MI (other than recent ACS event listed above)
- History of ischemic stroke
- Symptomatic peripheral arterial disease (history of claudication with ABI <0.85 or previous revascularization or amputation)

ABI = ankle-brachial index.

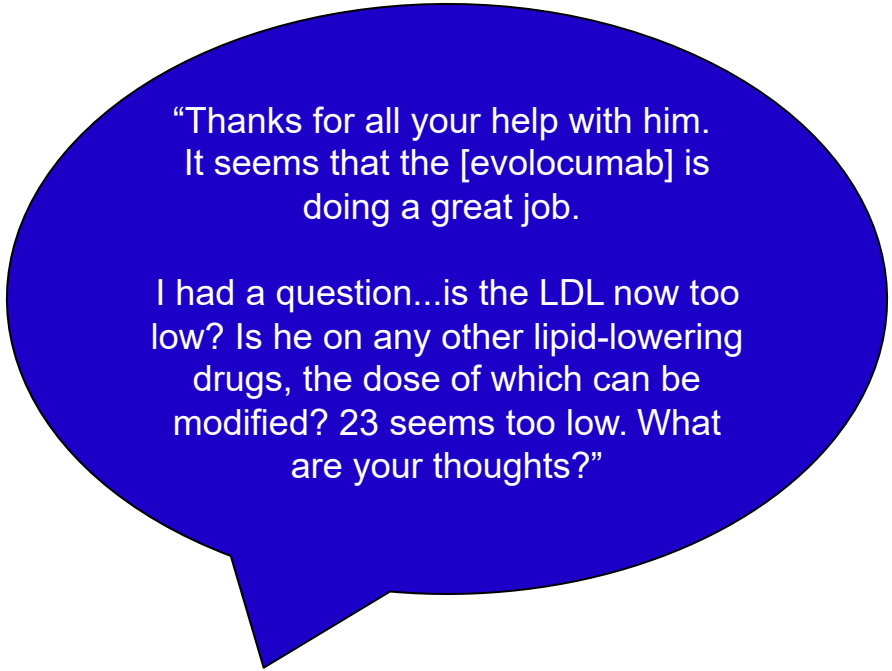
Grundy SM, et al. *Circulation*. 2019;139(25):e1082-e1143.

AHA/ACC Guidelines: Tailoring Treatment by Risk in Secondary Prevention



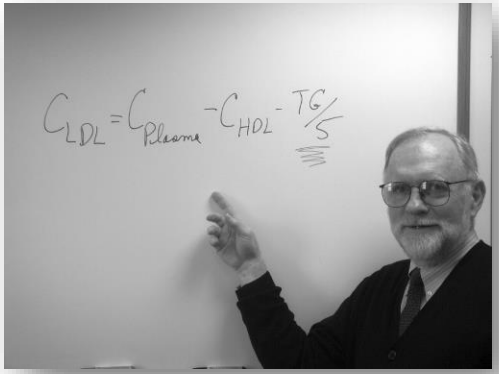
Grundy SM, et al. *Circulation*. 2019;139(25):e1082-e1143.

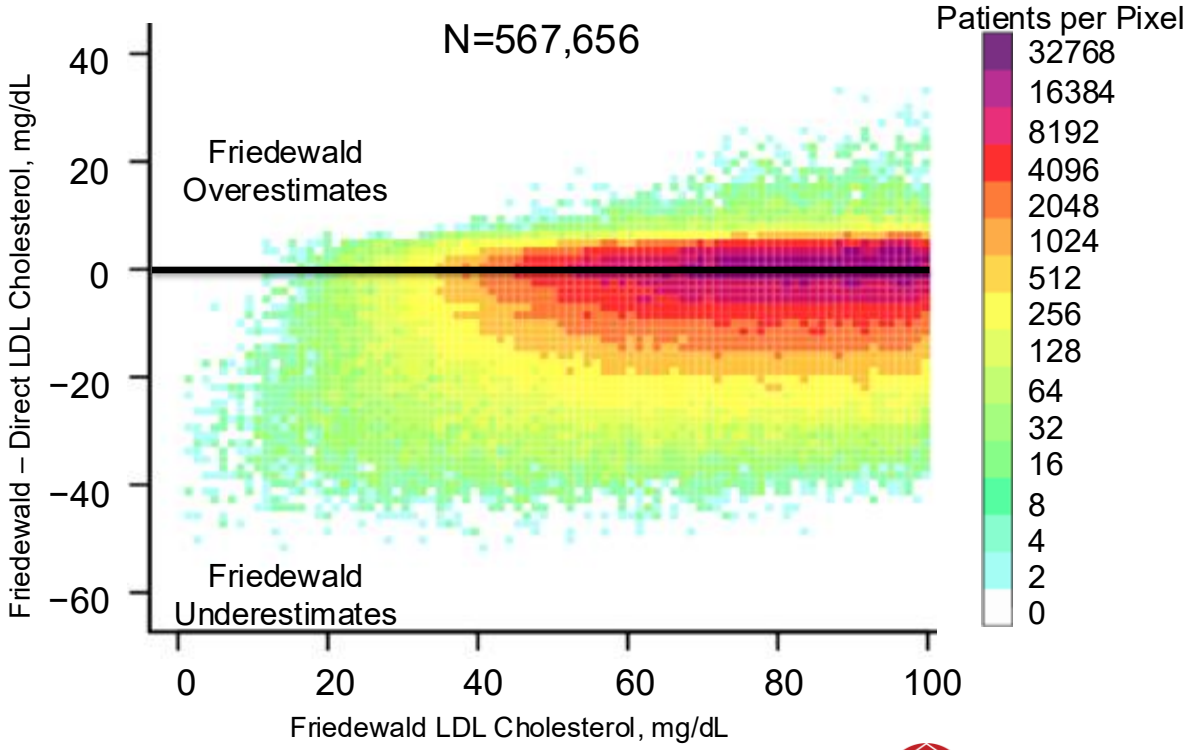
LDL-C Lowering: How Low Can We Go?



The Friedewald Equation Can Underestimate LDL-C

"Simple division of the plasma TG by 5 does not give a very accurate estimate of VLDL-C."



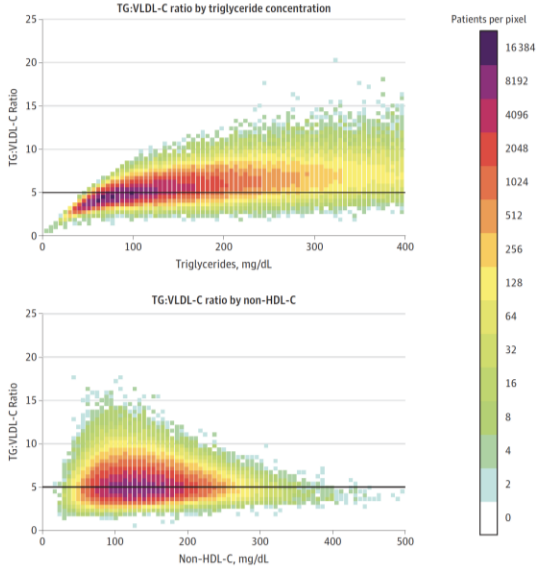


Friedewald WT, et al. *Clin Chem*. 1972;18(6):499-502. Martin SS, et al. *J Am Coll Cardiol*. 2013;62(8):732-739.

Practical Updates in Primary Care

Precision Medicine Solution to Improve LDL-C

2/3 of variance on TG: VLDL-C explained by TG and non-HDL-C levels



LDL-C

=

TC - HDL-C

-

TG / novel factor

Figure 2. Median for the Ratio of Triglycerides to Very Low-Density Lipoprotein Cholesterol by Non–High-Density Lipoprotein Cholesterol and Triglyceride Strata (180-Cell)

Triglyceride Levels, mg/dL[a]	Non-HDL-C, mg/dL					
	<100	100-129	130-159	160-189	190-219	≥220
7-49	3.5	3.4	3.3	3.3	3.2	3.1
50-56	4.0	3.9	3.7	3.6	3.6	3.4
57-61	4.3	4.1	4.0	3.9	3.8	3.6
62-66	4.5	4.3	4.1	4.0	3.9	3.9
67-71	4.7	4.4	4.3	4.2	4.1	3.9
72-75	4.8	4.6	4.4	4.2	4.2	4.1
76-79	4.9	4.6	4.5	4.3	4.3	4.2
80-83	5.0	4.8	4.6	4.4	4.3	4.2
84-87	5.1	4.8	4.6	4.5	4.4	4.3
88-92	5.2	4.9	4.7	4.6	4.4	4.3
93-96	5.3	5.0	4.8	4.7	4.5	4.4
97-100	5.4	5.1	4.8	4.7	4.5	4.3
101-105	5.5	5.2	5.0	4.7	4.6	4.5
106-110	5.6	5.3	5.0	4.8	4.6	4.5
111-115	5.7	5.4	5.1	4.9	4.7	4.5
116-120	5.8	5.5	5.2	5.0	4.8	4.6
121-126	6.0	5.5	5.3	5.0	4.8	4.6
127-132	6.1	5.7	5.3	5.1	4.9	4.7
133-138	6.2	5.8	5.4	5.2	5.0	4.7
139-146	6.3	5.9	5.6	5.3	5.0	4.8
147-154	6.5	6.0	5.7	5.4	5.1	4.8
155-163	6.7	6.2	5.8	5.4	5.2	4.9
164-173	6.8	6.3	5.9	5.5	5.3	5.0
174-185	7.0	6.5	6.0	5.7	5.4	5.1
186-201	7.3	6.7	6.2	5.8	5.5	5.2
202-220	7.6	6.9	6.4	6.0	5.6	5.3
221-247	8.0	7.2	6.6	6.2	5.9	5.4
248-292	8.5	7.6	7.0	6.5	6.1	5.6
293-399	9.5	8.3	7.5	7.0	6.5	5.9
400-13975	11.9	10.0	8.8	8.1	7.5	6.7

Martin SS, et al. *JAMA*. 2013;310(19):2061-2068.

Practical Updates in Primary Care

Expert Recommendations around the Globe

AHA

CHOLESTEROL CLINICAL PRACTICE GUIDELINES

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

ACC

EXPERT CONSENSUS DECISION PATHWAY

2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

National Lipid Association (NLA)

Lipid measurements in the management of cardiovascular diseases: Practical recommendations a scientific statement from the national lipid association writing group

European Atherosclerosis Society (EAS)

Clin Chem Lab Med 2020; 58(4): 496–517 DE GRUYTER

EFLM Consensus Paper

Michel R. Langlois*, Børge G. Nordestgaard, Anne Langsted, M. John Chapman, Kristin M. Aakre, Hannsjörg Baum, Jan Borén, Eric Bruckert, Alberico Catapano, Christa Cobbaert, Paul Collinson, Olivier S. Descamps, Christopher J. Duff, Arnold von Eckardstein, Angelika Hammerer-Lercher, Pia R. Kamstrup, Genovefa Kolovou, Florian Kronenberg, Samia Mora, Kari Pulkki, Alan T. Remaley, Nader Rifai, Emilio Ros, Sanja Stankovic, Ana Stavljenic-Rukavina, Grazyna Sypniewska, Gerald F. Watts, Olov Wiklund and Päivi Laitinen, for the European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Joint Consensus Initiative

Quantifying atherogenic lipoproteins for lipid-lowering strategies: consensus-based recommendations from EAS and EFLM

Special Article

Sociedade Brasileira de Cardiologia (SBC)

Positioning about the Flexibility of Fasting for Lipid Profiling

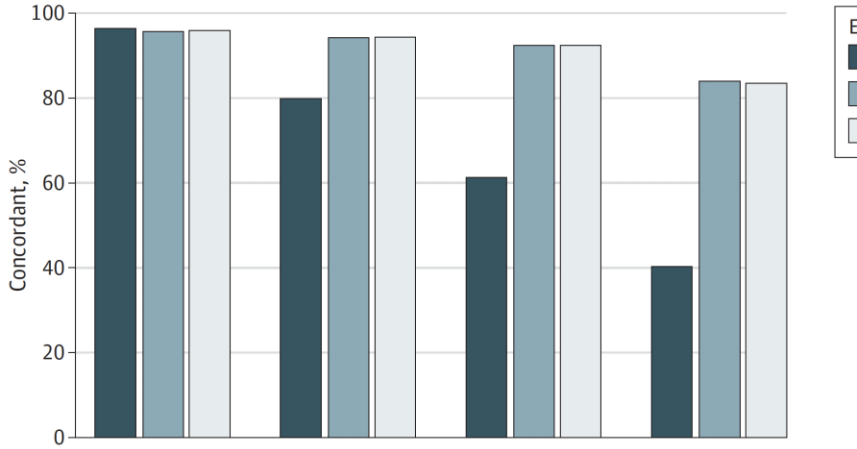
Marileia Scartezini,[1] Carlos Eduardo dos Santos Ferreira,[2] Maria Cristina Oliveira Izar,[3] Marcello Bertoluci,[4] Sergio Vencio,[5] Gustavo Aguiar Campana,[2] Nairo Massakazu Sumita,[2] Luiz Fernando Barcelos,[1] André A. Faludi,[3] Raul D. Santos,[3] Marcus Vinícius Bolívar Malachias,[3] Jerolino Lopes Aquino,[1] César Alex de Oliveira Galoro,[2] Cleide Sabino,[4] Maria Helane Costa Gurgel,[4] Luiz Alberto Andreotti Turatti,[5] Alexandre Hohl,[4] Tania Leme da Rocha Martinez[3]

Polish Lipid Association (PoLA)

PoLA/CFPiP/PCS/PSLD/PSD/PSH guidelines on diagnosis and therapy of lipid disorders in Poland 2021

Grundy SM, et al. *Circulation*. 2019;139(25):e1082-e1143. Lloyd-Jones DM, et al. *J Am Coll Cardiol*. 2022;80(14):1366-1418. Wilson PWF, et al. *J Clin Lipidol*. 2021;15(5):629-648. Langlois MR, et al. *Clin Chem Lab Med*. 2020;58(4):496-517. Banach M, et al. *Arch Med Sci*. 2021;17(6):1447-1547. Scartezini M, et al. *Arq Bras Cardiol*. 2017;108(3):195-197.

Accuracy >80% in Classifying LDL-C <70 mg/dL, Even at Elevated TG Levels



Triglyceride Category, mg/dL	<100	100 to 149	150 to 199	200 to 399
No. concordant/No. in group				
LDL-C_F	25 663/26 588	13 800/17 282	5695/9297	4483/11 116
LDL-C_{180}	25 739/27 928	13 016/13 807	4996/5407	3761/4476
LDL-C_{360}	25 679/27 778	12 990/13 748	4995/5404	3769/4512

Martin SS, et al. *JAMA*. 2013;310(19):2061-2068.

Practical Updates in Primary Care

LDL-C Equation Performance in FOURIER Trial of PCSK9 Inhibitor-Treated Patients Spanning 49 Countries

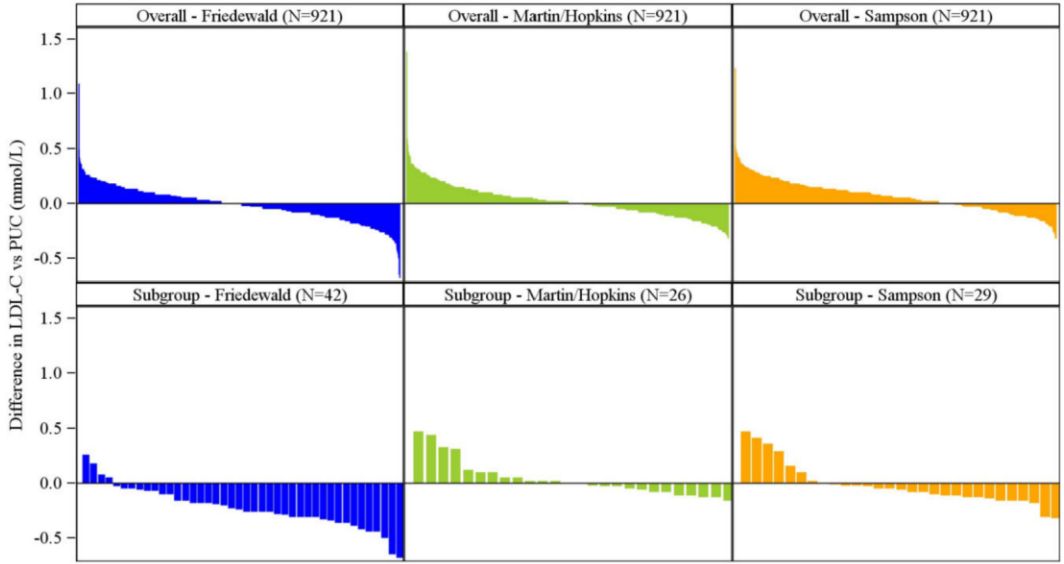
Difference in LDL-C between Estimated and Preparative Ultracentrifugation (Beta Quant)

Value Range, mg/dL	Absolute Difference, % (Overestimation, %/Underestimation, %)					
	All Patients With Friedewald LDL-C <40 mg/dL (n = 12 742 Patients; n = 56 624 Observations)		*P* Value	Patients With Friedewald LDL-C <40 mg/dL and TG ≥150 mg/dL (n = 11 991 Observations)		*P* Value
	Martin/Hopkins	Friedewald		Martin/Hopkins	Friedewald	
≤5	77.1 (23.2/53.9)	59.9 (13.0/46.9)		68.0 (35.0/33.0)	17.2 (2.2/15.1)	
>5-10	20.3 (5.2/15.1)	26.8 (0.8/26.1)		21.9 (17.1/4.9)	32.5 (0.4/32.1)	
>10-20	2.3 (1.9/0.4)	11.7 (0.1/11.7)	<.001	8.4 (8.3/0.2)	43.0 (0.3/42.7)	<.001
>20-30	0.3 (0.3/<0.01)	1.4 (0.02/1.4)		1.3 (1.3/<0.01)	6.6 (0.1/6.5)	
>30	0.1 (0.1/<0.01)	0.1 (<0.01/0.1)		0.3 (0.3/<0.01)	0.7 (<0.01/0.7)	

Martin SS, et al. *JAMA Cardiol*. 2018;3(8):749-753.

Practical Updates in Primary Care

LDL-C Equation Performance Compared to Beta Quant in the TULIP Trial of Obicetrapib



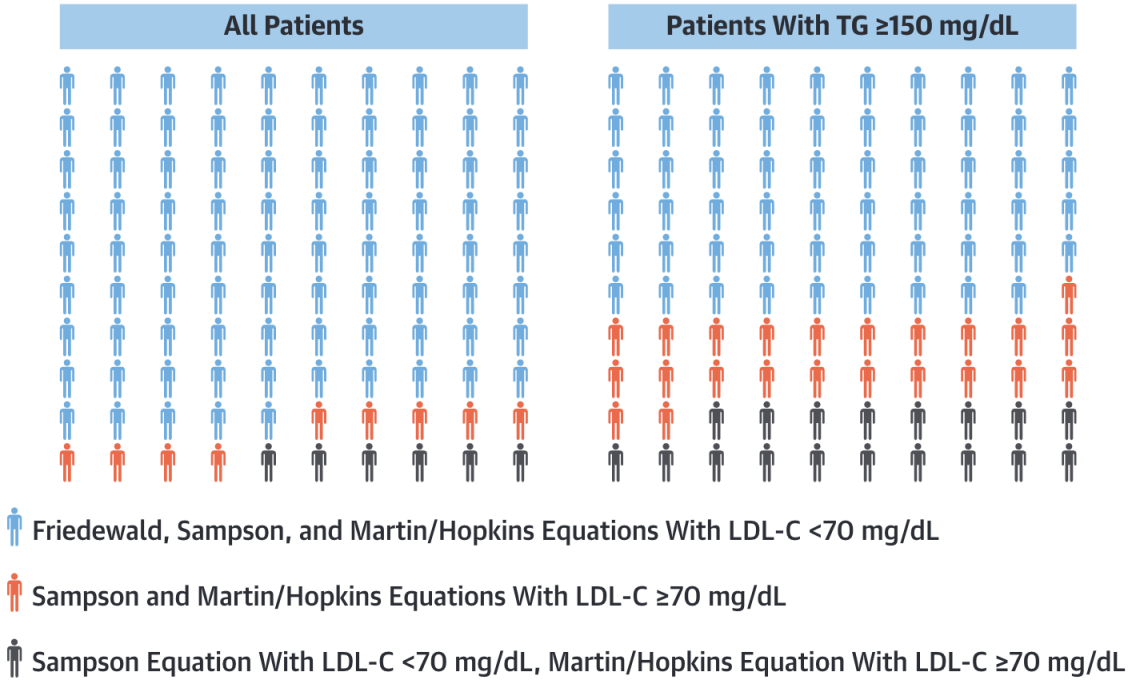
In patients with LDL-C <70 mg/dL, correct classification compared with beta quant

- Friedewald – 71.4%
- Martin/Hopkins – 100%
- Sampson – 93.1%

Martin SS, et al. *Eur Heart J Cardiovasc Pharmacother*. 2023;9(2):148-155.

Practical Updates in Primary Care

Missed Opportunities for Treatment Intensification due to LDL-C Underestimation



Sajja A, et al. *J Am Coll Cardiol*. 2022;79(6):530-541.

Practical Updates in Primary Care

Safety of Very Low LDL-C: FOURIER

	LDL-cholesterol concentration at 4 weeks					p_{trend}
	<0·5 mmol/L (n=2669)	0·5 to <1·3 mmol/L (n=8003)	1·3 to <1·8 mmol/L (n=3444)	1·8 to <2·6 mmol/L (n=7471)	≥2·6 mmol/L (n=4395)	
Serious adverse events	614 (23%)	1948 (24%)	838 (24%)	1684 (23%)	1022 (23%)	0·13
Adjusted OR (95% CI)	0·97 (0·86–1·10)	1·01 (0·92–1·11)	1·01 (0·90–1·13)	0·93 (0·84–1·02)	1 (ref)	0·30
Adverse events* leading to discontinuation of study drug	98 (4%)	295 (4%)	124 (4%)	234 (3%)	149 (3%)	0·11
Adjusted OR (95% CI)	1·08 (0·82–1·43)	1·07 (0·86–1·33)	1·07 (0·83–1·39)	0·91 (0·73–1·14)	1 (ref)	0·13
AST or ALT elevation (>3 times ULN)	41 (2%)	120 (1%)	76 (2%)	119 (2%)	83 (2%)	0·19
Adjusted OR (95% CI)	0·96 (0·64–1·43)	0·87 (0·64–1·17)	1·25 (0·90–1·74)	0·91 (0·68–1·24)	1 (ref)	0·64
Creatine kinase elevation (>5 times ULN)	18 (1%)	55 (1%)	19 (1%)	58 (1%)	26 (1%)	0·99
Adjusted OR (95% CI)	1·02 (0·53–1·96)	1·07 (0·65–1·77)	0·88 (0·47–1·65)	1·23 (0·75–2·02)	1 (ref)	0·72
Neurocognitive events	49 (2%)	122 (2%)	51 (1%)	100 (1%)	52 (1%)	0·019
Adjusted OR (95% CI)	1·28 (0·84–1·96)	1·10 (0·78–1·55)	1·10 (0·73–1·65)	0·97 (0·68–1·39)	1 (ref)	0·15
New onset diabetes mellitus†	135/1655 (8%)	389/4863 (8%)	162/1886 (9%)	356/4603 (8%)	220/2778 (8%)	0·63
Adjusted OR (95% CI)	1·06 (0·83–1·35)	1·00 (0·83–1·20)	1·03 (0·83–1·30)	0·95 (0·78–1·14)	1 (ref)	0·48
Cataract-related adverse events	56 (2%)	124 (2%)	61 (2%)	134 (2%)	55 (1%)	0·15
Adjusted OR (95% CI)	1·54 (1·03–2·31)	1·14 (0·82–1·60)	1·34 (0·91–1·98)	1·35 (0·96–1·89)	1 (ref)	0·43
New or progressive malignancy	64 (2%)	205 (3%)	87 (3%)	166 (2%)	99 (2%)	0·22
Adjusted OR (95% CI)	0·90 (64–1·27)	1·01 (0·78–1·31)	1·04 (0·77–1·42)	0·88 (0·67–1·15)	1 (ref)	0·72
Haemorrhagic stroke	3 (<1%)	19 (<1%)	7 (<1%)	17 (<1%)	7 (<1%)	0·99
Adjusted HR (95% CI)	0·71 (0·17–2·90)	1·55 (0·62–3·85)	1·39 (0·47–4·14)	1·57 (0·62–3·98)	1 (ref)	0·91
Non-cardiovascular death	25 (1%)	86 (1%)	34 (1%)	66 (1%)	45 (1%)	0·67
Adjusted HR (95% CI)	0·89 (0·53–1·50)	1·06 (0·72–1·55)	1·03 (0·65–1·64)	0·89 (0·60–1·33)	1 (ref)	0·73

Data are n (%) or n/N (%), unless otherwise specified. OR=odds ratio. ref=reference. AST=aspartate aminotransferase. ALT=alanine aminotransferase. ULN=upper limit of normal. HR=hazard ratio.
*Excludes 17 patients with injection-site reactions. †Denominator excludes patients who were diagnosed with diabetes mellitus before the week-4 visit.

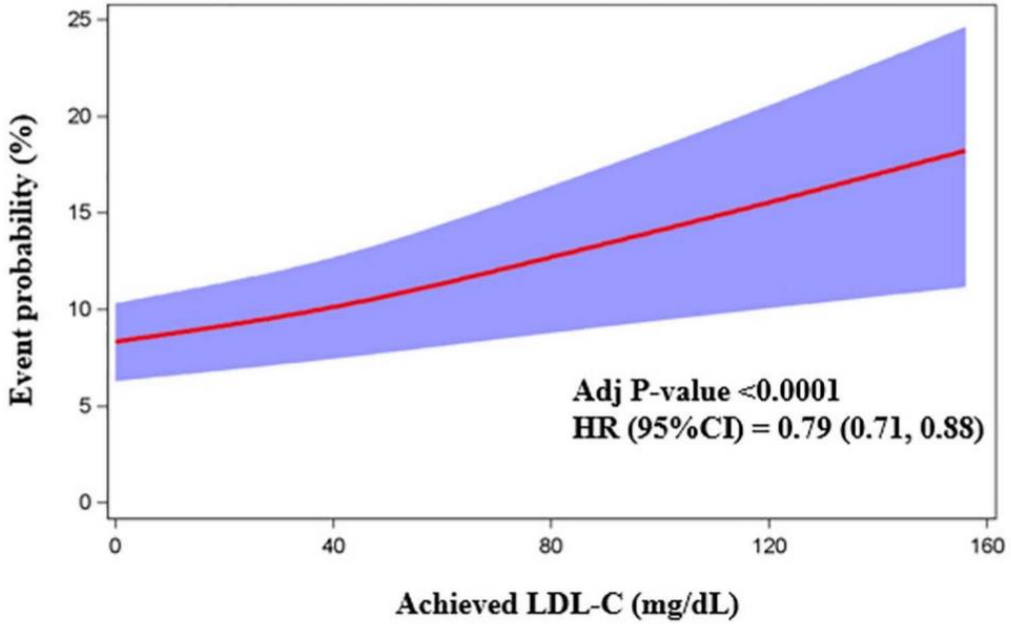
Table 2: Safety events by achieved LDL-cholesterol concentration at 4 weeks after randomisation

- No safety concerns with very low LDL-C over 2.2 yrs on evolocumab treatment
- No excess in new-onset diabetes, cataracts, hemorrhagic stroke, or other safety events, even in patients achieving LDL-C <0.5 mmol/L (<20 mg/dL)

Giugliano RP, et al. *Lancet*. 2017;390(10106):1962-1971.

Practical Updates in Primary Care

FOURIER-OLE with Follow-Up through 8.6 Years: Lower for Longer Is Better

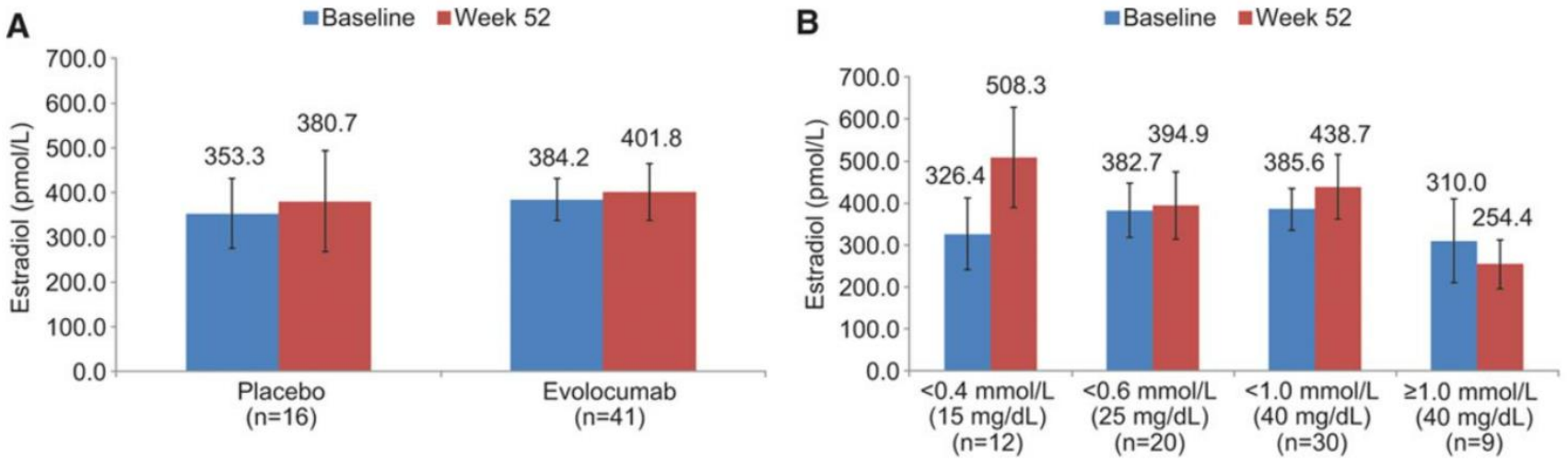


No statistically significant associations existed in the primary analyses between lower achieved LDL-C levels and increased risk of the safety outcomes

Gaba P, et al. *Circulation*. 2023;147(16):1192-1203.

Practical Updates in Primary Care

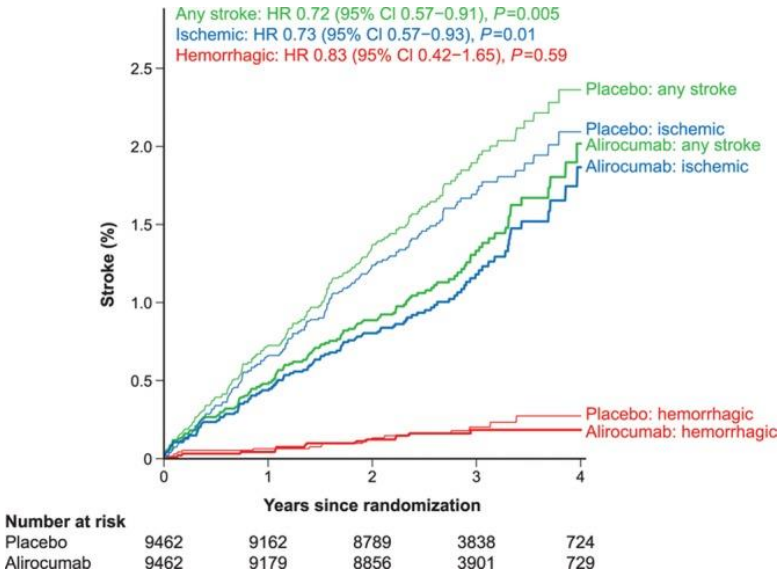
Effect of Evolocumab on Steroid and Gonadal Hormone Levels: The DESCARTES Trial



No adverse effects were observed in steroid or gonadal hormones, even at very low LDL-C levels

Blom DJ, et al. *Circ Res.* 2015;117(8):731-741.

Risk of Hemorrhagic Stroke with Intensive LDL-C Lowering



Month 4 LDL-C, mg/dL	n/N (%)
<25	2/3399 (0.1)
25 to <50	3/3754 (0.1)
50 to <70	3/1090 (0.3)
≥70	4/1177 (0.3)

Achievement of Very Low Low-Density Lipoprotein Cholesterol Levels

Is It Time to Unlearn Concern for Hemorrhagic Stroke?

Erin D. Michos and **Seth S. Martin**

Originally published 11 Nov 2019 | https://doi.org/10.1161/CIRCULATIONAHA.119.044275 | Circulation. 2019;140:2063–2066

Jukema JW, et al. *Circulation*. 2019;140(25):2054-2062.

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Key Learning Points

- Combination lipid-lowering therapy enables achievement of low LDL-C, even when starting high
- Be mindful of the LDL-C equation to avoid undertreatment
- There is no apparent lower safety limit for LDL-C levels
- Individualize treatment based on
  - Risk
  - Tolerance
  - Efficacy
  - Patient preference
  - Cost

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Section 4: Addressing Barriers to Optimal Lipid-Lowering Therapy

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Barriers to Optimal Lipid-Lowering Therapy

- Risk-assessment bias
- Atherosclerosis is silent; can be catastrophic
- Public health messaging
- Popular/social media messaging
- Time constraints in clinic
- Shared goals
- Optimal messaging
- Optimal treatments

Preventive Pharmacotherapies Must Be…

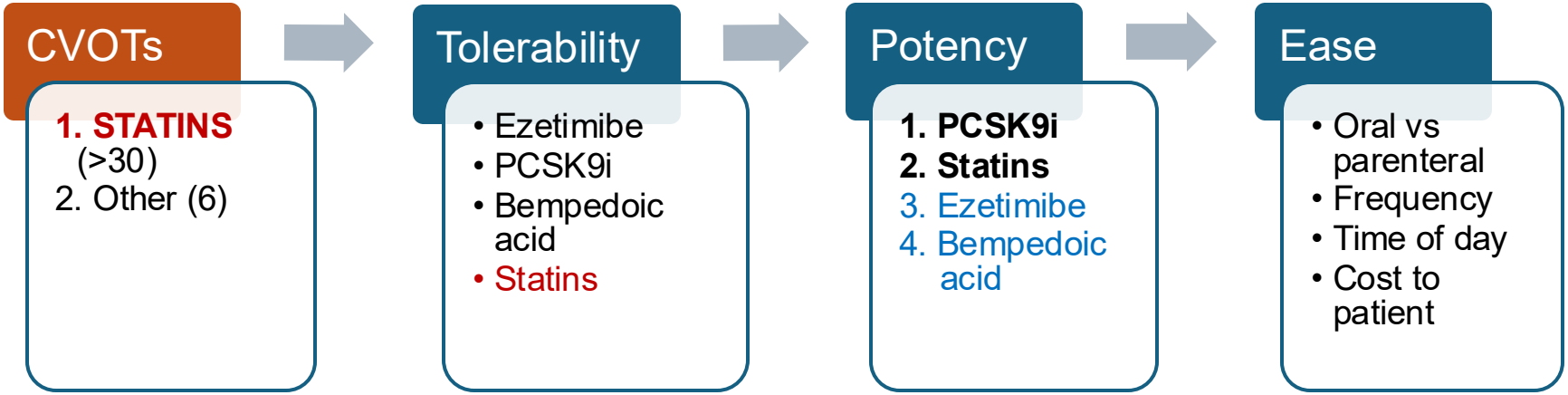
- Safe
- Well-tolerated
- Effective
- Evidence-based
- Guideline-based
- Affordable
- Available
- Agreeable to patients and clinicians

Selecting LDL-Lowering Rx; “Safety”

	Common	Rare
Statins	Hyperglycemia	Rhabdomyolysis Statin-associated necrotizing myositis (immune-mediated)
Ezetimibe		
PCSK9i		
Bempedoic acid	Hyperuricemia Elevated BUN and Cr	Tendon injury
Bile acid sequestrant	Constipation/obstipation	

BUN = blood urea nitrogen.

Selecting LDL-Lowering Rx



CVOTs = cardiovascular outcomes trials.

Achieved LDL-C and ApoB Levels in Non-Statin CVOTs (2015-2023)

	IMPROVE-IT **(2015)**	FOURIER **(2017)**	ODYSSEY Outcomes **(2018)**	CLEAR Outcomes **(2023)**
Patient population	ACS	Stable ASCVD	ACS	Stable ASCVD or high-risk primary prevention
Background therapy	Moderate-intensity statin (simvastatin)	High-intensity statin +/- ezetimibe	High-intensity statin +/- ezetimibe	Low-intensity or no statin
Intervention	Ezetimibe (oral) 10 mg daily	Evolocumab (SQ) 140 mg every 2 wks	Alirocumab (SQ) 75 or 150 mg every 2 wks; adjusted dose targeting LDL-C 25-50 mg/dL	Bempedoic acid (oral) 180 mg daily
N	18,144	27,564	18,924	13,970
Achieved LDL-C (mean): Placebo vs intervention (mg/dL)	70 vs **54**	92 vs **30**	92 vs **48**	139 vs **110** (at 6 months); 124 vs **103** (at 60 months)[#]
Achieved ApoB (mean): Placebo vs intervention (mg/dL)	79 vs 67	83 vs 38	83 vs 49	n/a
RRR (median duration)	6.4% (6+ yrs)	15% (2.2 yrs)	15% (2.8 yrs)	13% (3.4 yrs)

[#]All imputed from reported percentile reduction.
RRR = relative risk reduction.

Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-2397. Sabatine MS, et al. *N Engl J Med*. 2017;376(18):1713-1722. Schwartz GG, et al. *N Engl J Med*. 2018;379(22):2097-2107. Nissen SE, et al. *N Engl J Med*. 2023;388(15):1353-1364.

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Guideline/Consensus Statement Thresholds/Goals (AHA, ACC, NLA)

Risk group	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	ApoB (mg/dL)
Very high	<55	<85	<60
High	<70	<100	<70
Intermediate	<100	<130	<90

Grundy SM, et al. *J Am Coll Cardiol*. 2019;73(24):3168-3209. Lloyd-Jones DM, et al. *J Am Coll Cardiol*. 2022;80(14):1366-1418. Soffer DE, et al. *J Clin Lipidol*. 2024;18(5):e647-e663.

Key Learning Points

- Identify goals of care
- Know the evidence/guidelines
- Review best options for the individual