LDL-C in Managing High-risk ASCVD Patients: Current Gaps & Paradigms

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Disclosures

- Consultant to Sanofi, Novo-Nordisk, Novartis, Boehringer-Ingelheim, Amgen, Bayer, Medtronic, Merck, Edwards, Jazz and Esperion. Founder and Shareholder of Epirium Bio

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  - Impact of time-restricted feeding (TRF) on glucose homeostasis and mitochondrial function in patients with metabolic syndrome – The TIMET Study (NCT0405733)
- Hillblom Network Grant (PI: Taub PR) (NCT05365529)
- Dysautonomia International Grant (PI: Taub PR) (NCT05409651)

Clinical Trial Leadership:

- US National Lead/Steering Committee Member for: Study of Inclisiran to Prevent Cardiovascular (CV) Events in Participants With Established Cardiovascular Disease (VICTORION-2P). (Sponsor: Novartis; NCT05030428)
- US National Lead/Steering Committee Member for: A Double-blind, Randomized, Placebo controlled, Multicenter Study Assessing the Impact of Olpasiran on Major Cardiovascular Events in Patients with Atherosclerotic Cardiovascular Disease and Elevated Lipoprotein (a). (Sponsor: Amgen NCT05581303)
- Global Executive Steering Committee Member for VICTORIAN-1P Trial (Sponsor: Novartis)
- National Principal Investigator for the NIH RECOVER COVID Initiative (recovercovid.org) and responsible for design and execution of studies related to Post COVID Postural Orthostatic Tachycardia Syndrome.
- US National Lead/Steering Committee Member for MK0616 (oral PCSK9 inhibitor) Phase 3 program (Sponsor: Merck)
- Executive Steering Committee Member for TRANSFORM Trial (Sponsor: Cleerly)

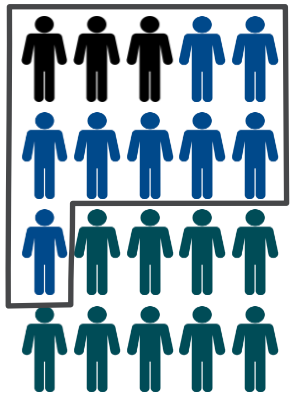
Outline

- Overview of the high-risk ASCVD patient
- Suboptimal LDL-C goal achievement in high-risk and very high-risk patients
- Updates from the ACC Expert Consensus Statement on Lipid Lowering
- Update on use of Coronary Calcium Score in refining LDL goals
- How low do we go?

Who Is the Very High-Risk ASCVD Patient?

- **Recent ACS**
- **History of prior MI or ischemic stroke**
- **Symptomatic PAD**
- Age ≥ 65 years
- HeFH
- Prior CABG or PCI
- Diabetes
- Hypertension

Among 27,775 patients with a history of ASCVD in the MarketScan database on January 1, 2016



55.3% met the definition for very high risk, or those

26.0% had multiple major ASCVD events

74.0% had a major ASCVD event and multiple high-risk conditions

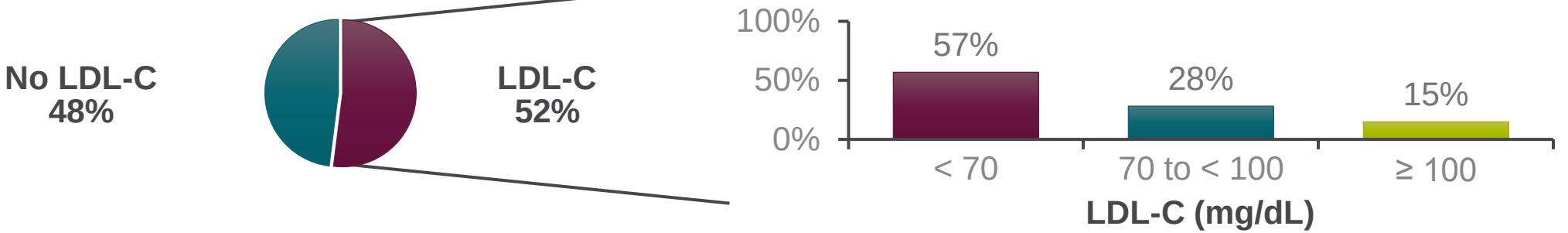
- Chronic kidney disease
- Current smoking
- LDL-C ≥ 100 mg/dL (2.6 mmol/L) despite maximally tolerated statin and ezetimibe
- History of HF
- Recurrent ASCVD events
- Major ASCVD event with ≥ 1 risk conditions

Colantonio LD, et al. *J Am Coll Cardiol.* 2019;74(20):2496-507;
Lloyd-Jones DM et al. *J Am Coll Cardiol.* 2022 DOI: 10.1016/j.jacc.2022.07.006

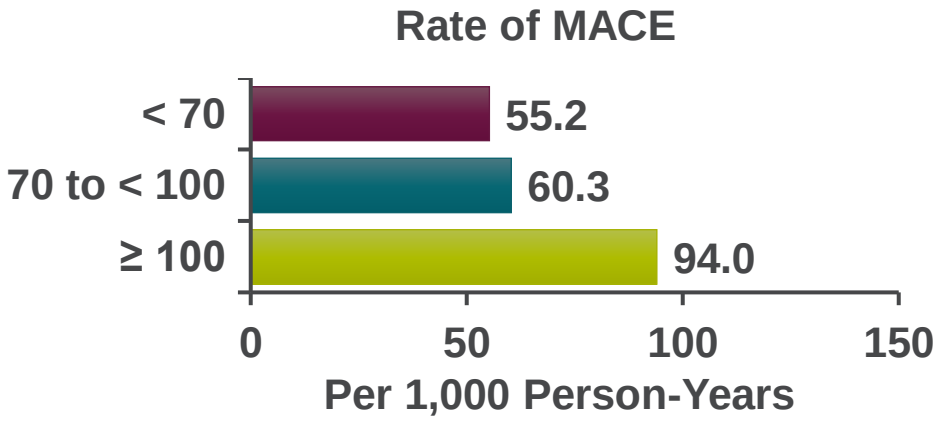
Reality Check:
Many Patients with ASCVD Not at LDL-C Goal

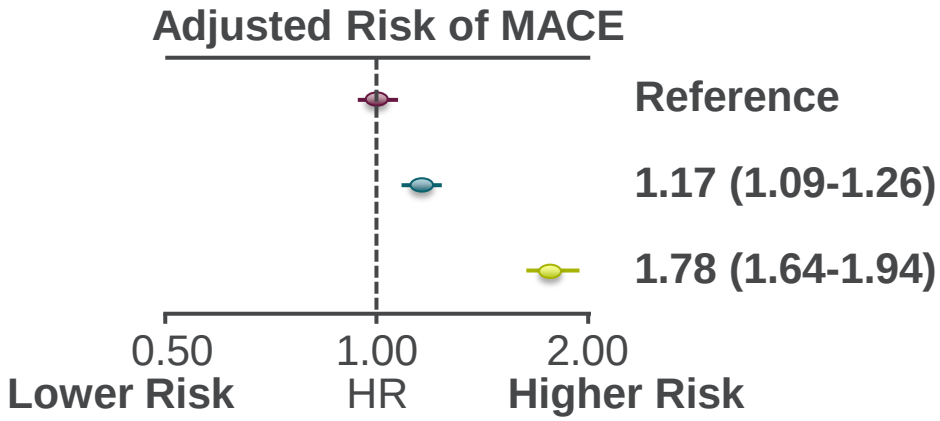
of every 2 patients had LDL-C measured after PCI

~1 of every 2 patients had LDL-C < 70 mg/dL



Higher LDL-C after PCI was associated with a higher risk of MACE



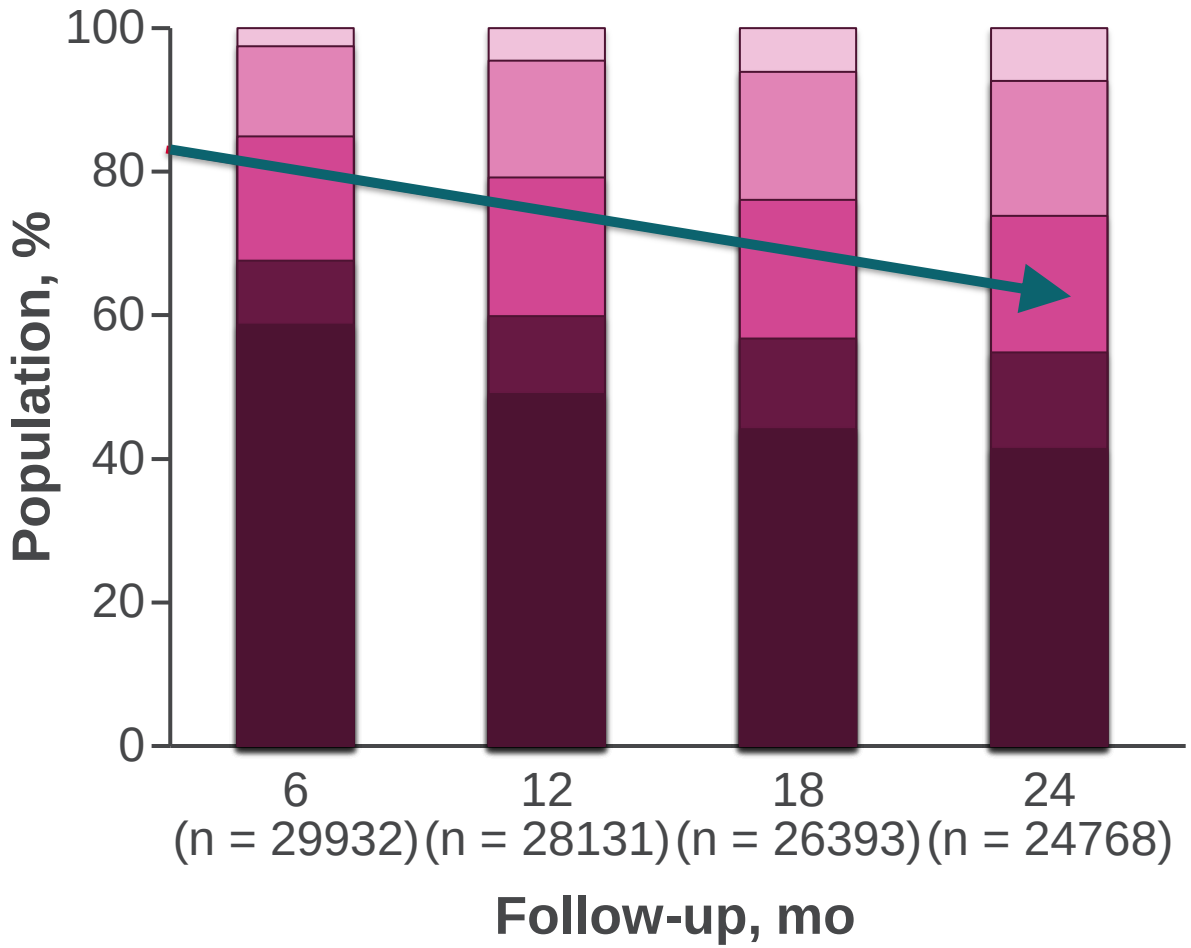


Sud M et al. *J Am Coll Cardiol*. 2020;76:1440-1450.

Pattern of Statin Use After Discharge for Myocardial Infarction *Among Medicare Beneficiaries 66 to 75 Years of Age (N = 29,932)*

Adherence to High-Intensity Statins Following a Myocardial Infarction Hospitalization Among Medicare Beneficiaries

- Remain taking high-intensity statins with high adherence
- Down-titrate to low/moderate-intensity statins with high adherence
- Statin use with low adherence
- Discontinuation of statins
- Other patterns of statin use



Colantonio et al. *JAMA Cardiol*. 2017;2(*):890-5.

GOULD Registry: High-Risk Patients with ASCVD

GOULD is a multicenter observational registry that describes lipid lowering therapy patterns among patients with clinical ASCVD + LDL-C ≥ 70 mg/dL (or taking a PCSK9i) in the United States

N = 5006

Enrolled from Dec 2016 - Jul 2018

Cohort 1

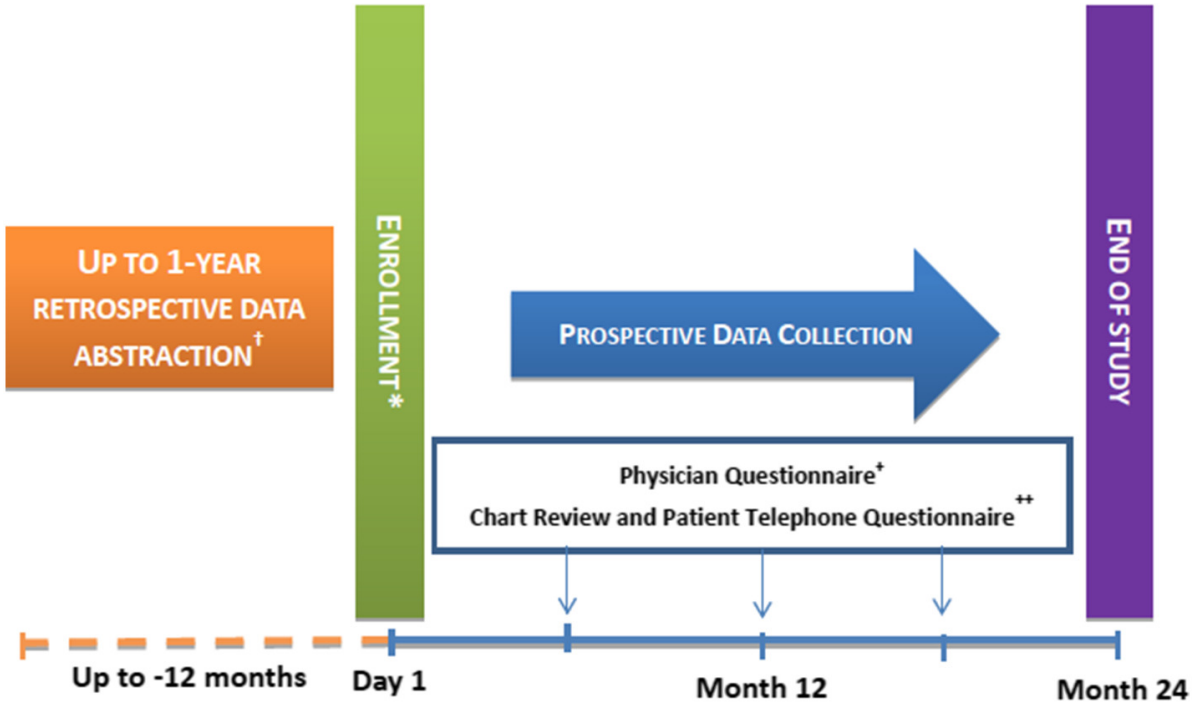
Patients taking PCSK9i at baseline

Cohort 2

Patients with LDL-C ≥ 100 mg/dL

Cohort 3

Patients with LDL-C 70–99 mg/dL



PCSK9i = Proprotein Convertase Subtilisin/Kexin type 9 Inhibitor

Cannon CP, et al. *Am Heart J.* 2020 ;219:70-77.

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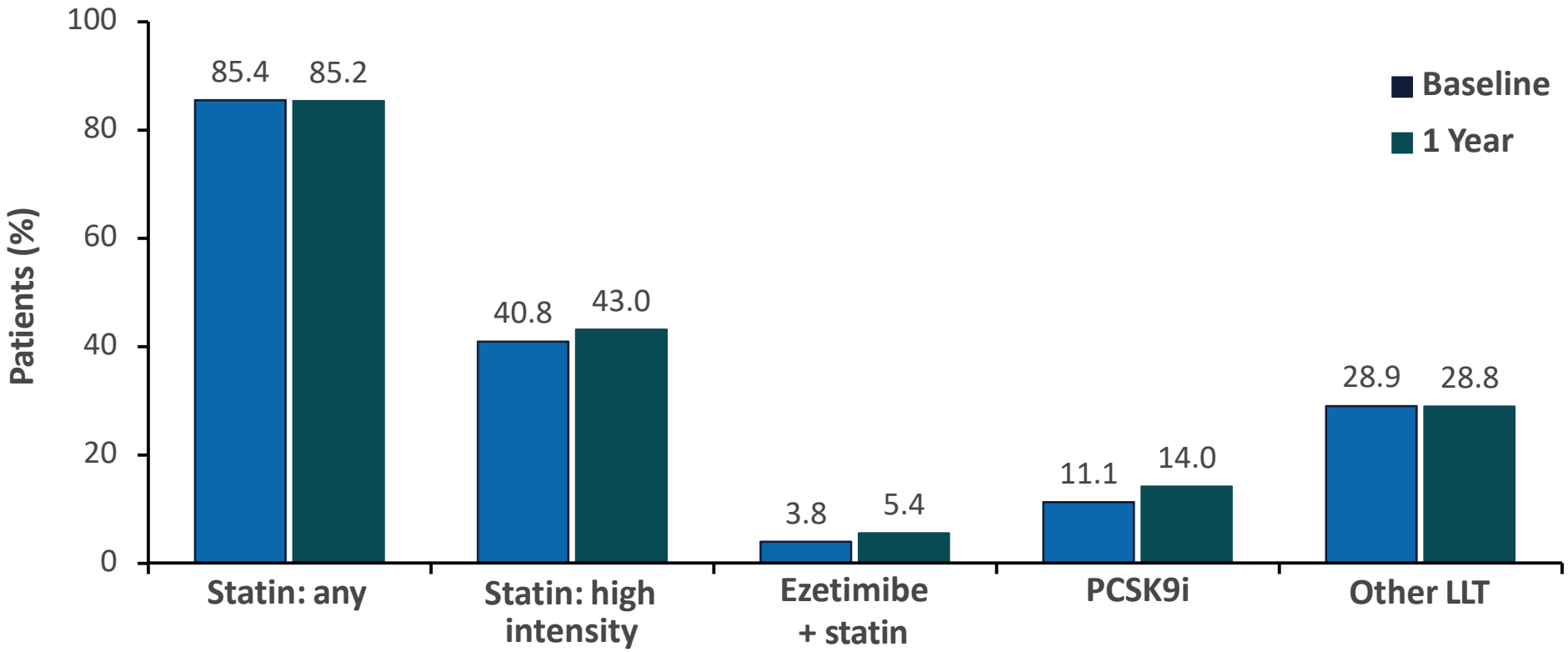
Gould: Use of Lipid Lower Therapies (LLT)



Cannon CP et al. *JAMA Cardiol.* 2021;6(9):1060-1068.

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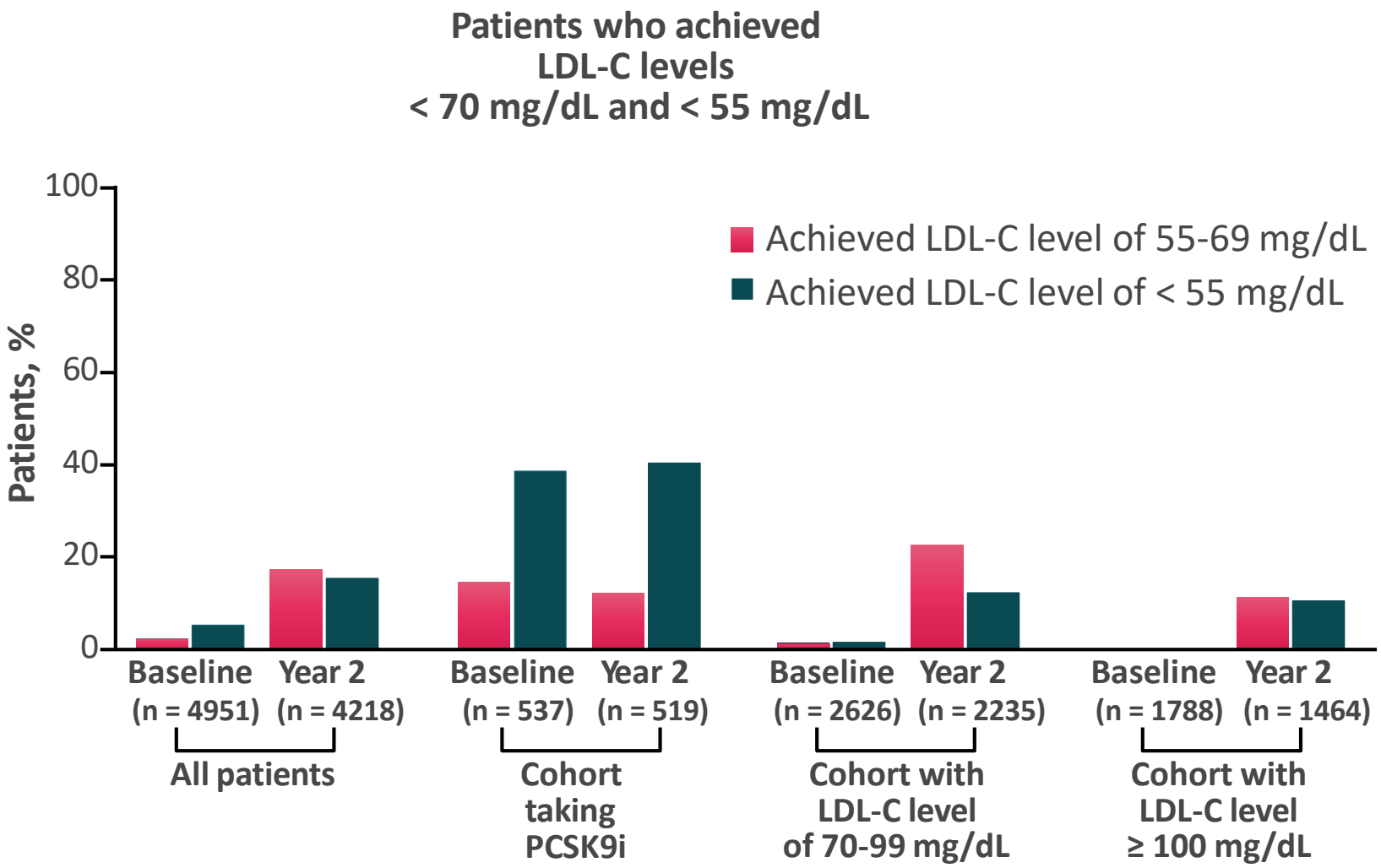
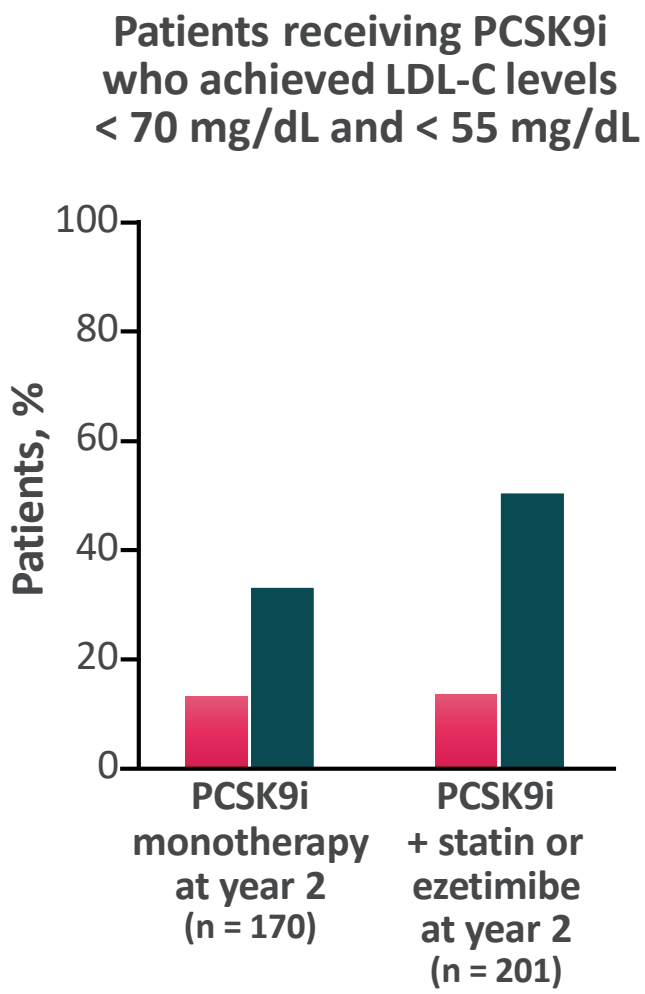
GOULD: Combination Therapy Required to Achieve Target LDL-C





Cannon CP et al. *JAMA Cardiol.* 2021;6(9):1060-1068.

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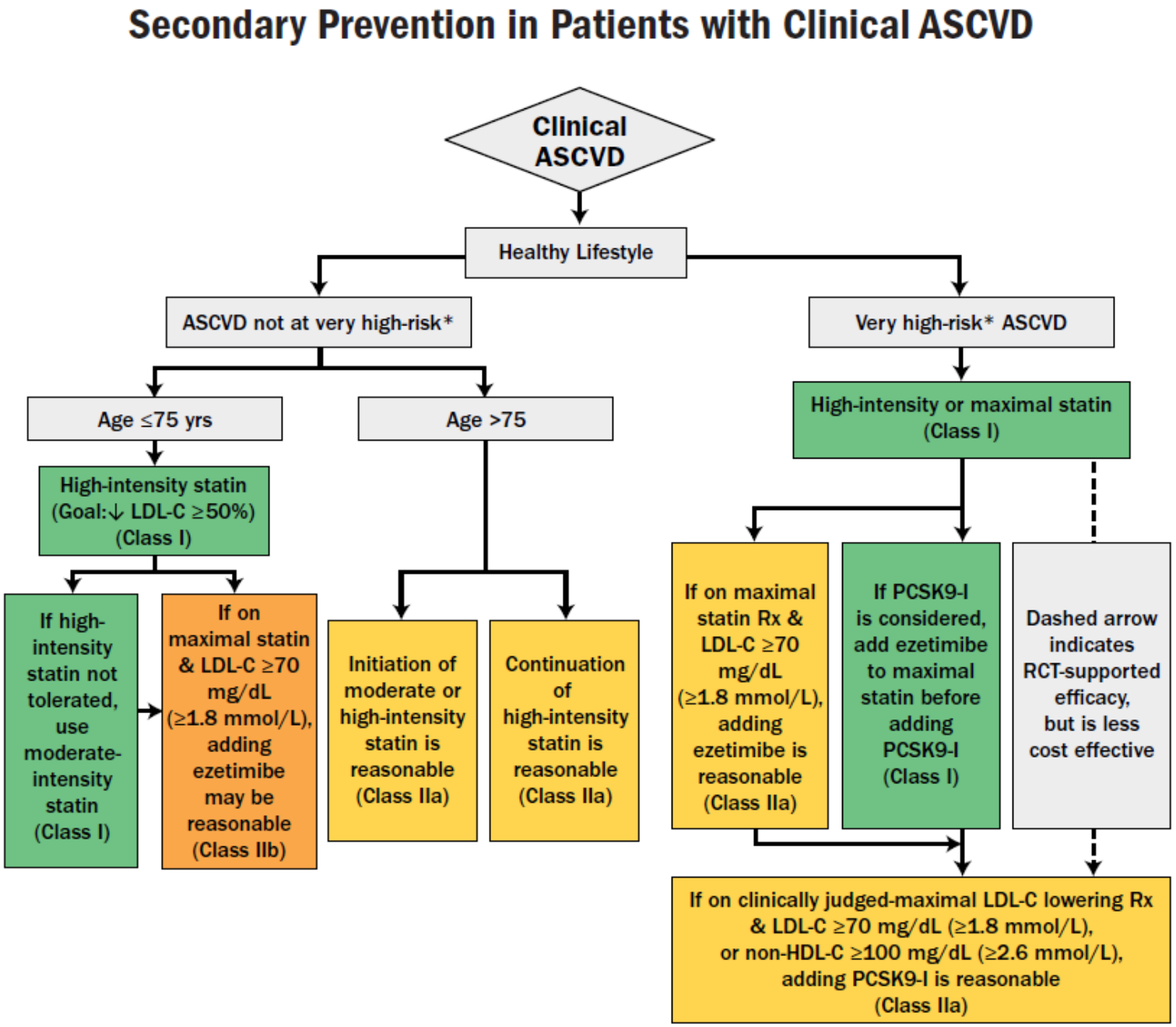
Very high-risk features

- Recent ACS
- History of prior MI
- History of ischemic stroke
- Symptomatic PAD

- Age ≥65 years
- HeFH
- Prior CABG or PCI
- Diabetes
- Hypertension
- Chronic kidney disease
- Current smoking
- LDL-C ≥ 2.6 mmol/L (100 mg/dL) on statin and ezetimibe
- History of HF

- Recurrent ASCVD events
- Major ASCVD event with ≥1 risk conditions



https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000624

- 48-y/o female
- **History:** Hypertension, metabolic syndrome, NSTEMI (1 week ago) with stent placement in proximal LAD
- **Family history:** Father with MI at age 42
- **Physical exam:**
  - BP 139/85 mmHg, HR 75 bpm, BMI 30 kg/m^2
  - 3/6 mid peaking systolic ejection murmur at RUSB
- **Meds:**
  - Lisinopril 20 mg qd, aspirin 81 mg qd, ticagrelor 90 mg bid, atorvastatin 80 mg qd (started during NSTEMI admission), metoprolol succinate 25 mg qd

Audience Response Question

- **Labs 2 months after discharge (on atorvastatin 80 mg)**
  - Total-C 261 mg/dL
  - LDL-C 120 mg/dL
  - HDL-C 40 mg/dL
  - Triglycerides 180 mg/dL
  - Lp(a) 200 mg/dL

What would you do next?

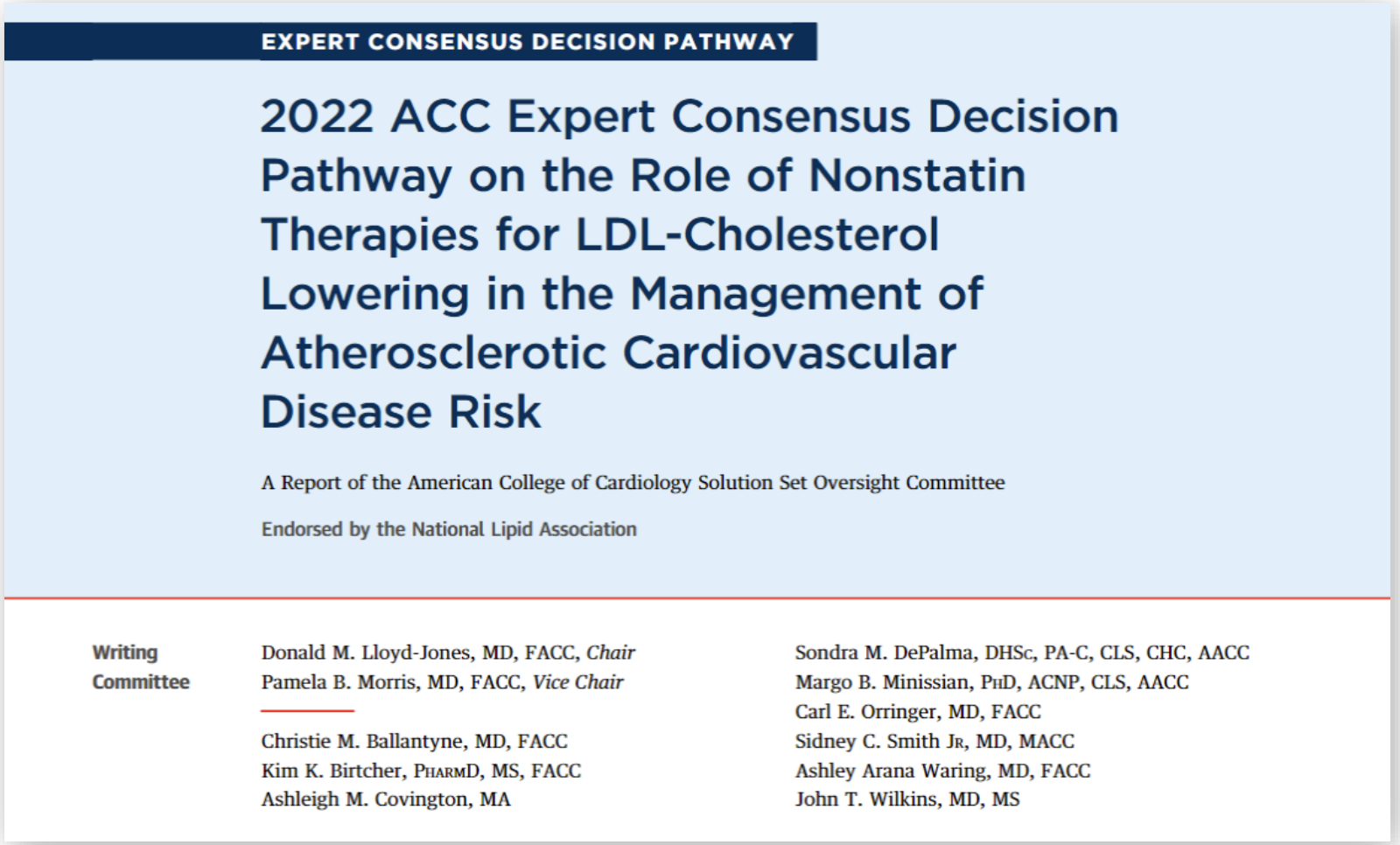
A) Add ezetimibe

B) Add icosapent ethyl

C) Add ezetimibe and alirocumab

D) Add bempedoic acid

Updated Recommendations for LDL-C Lowering



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

A Report of the American College of Cardiology Solution Set Oversight Committee

Endorsed by the National Lipid Association

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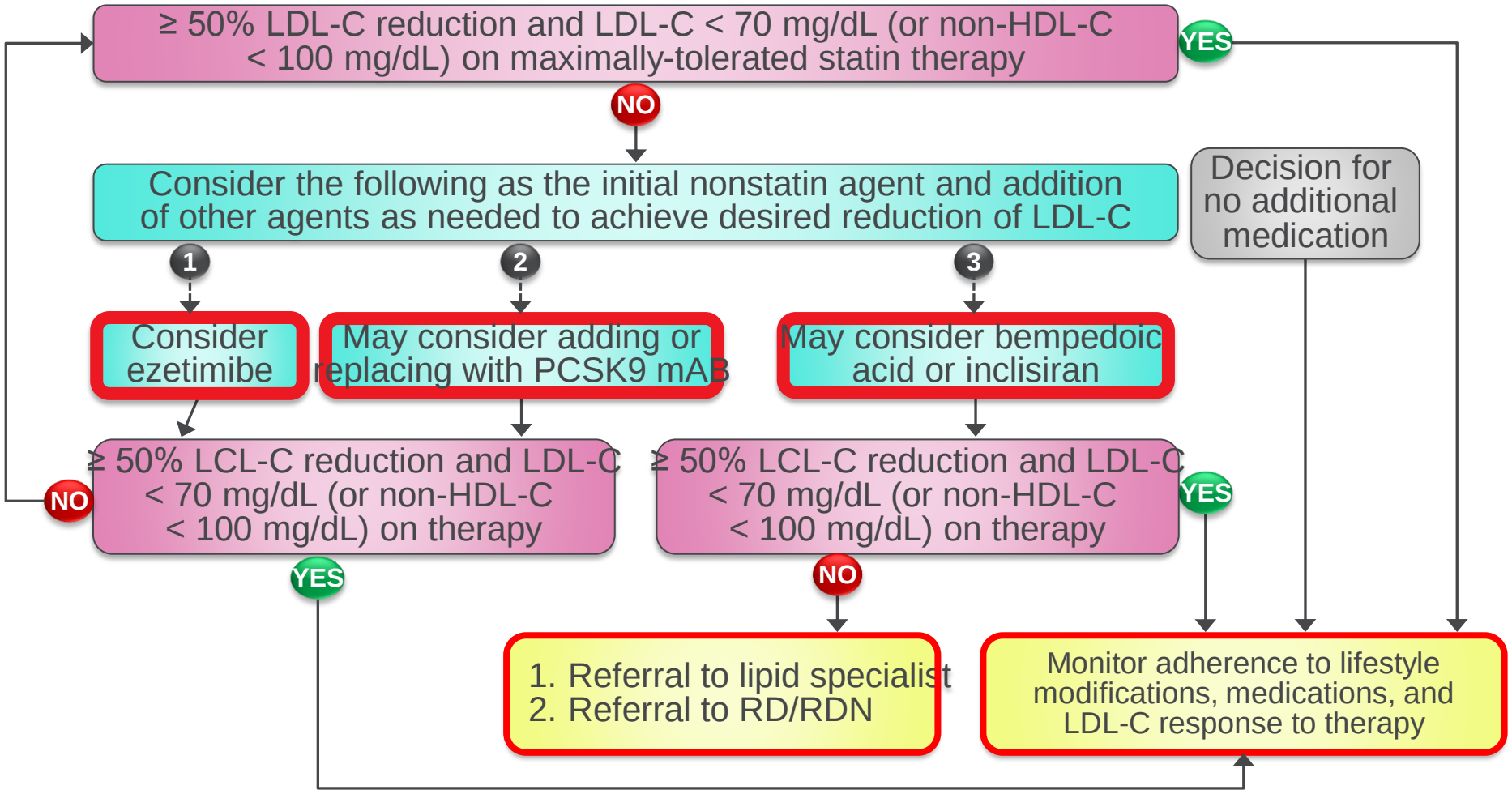
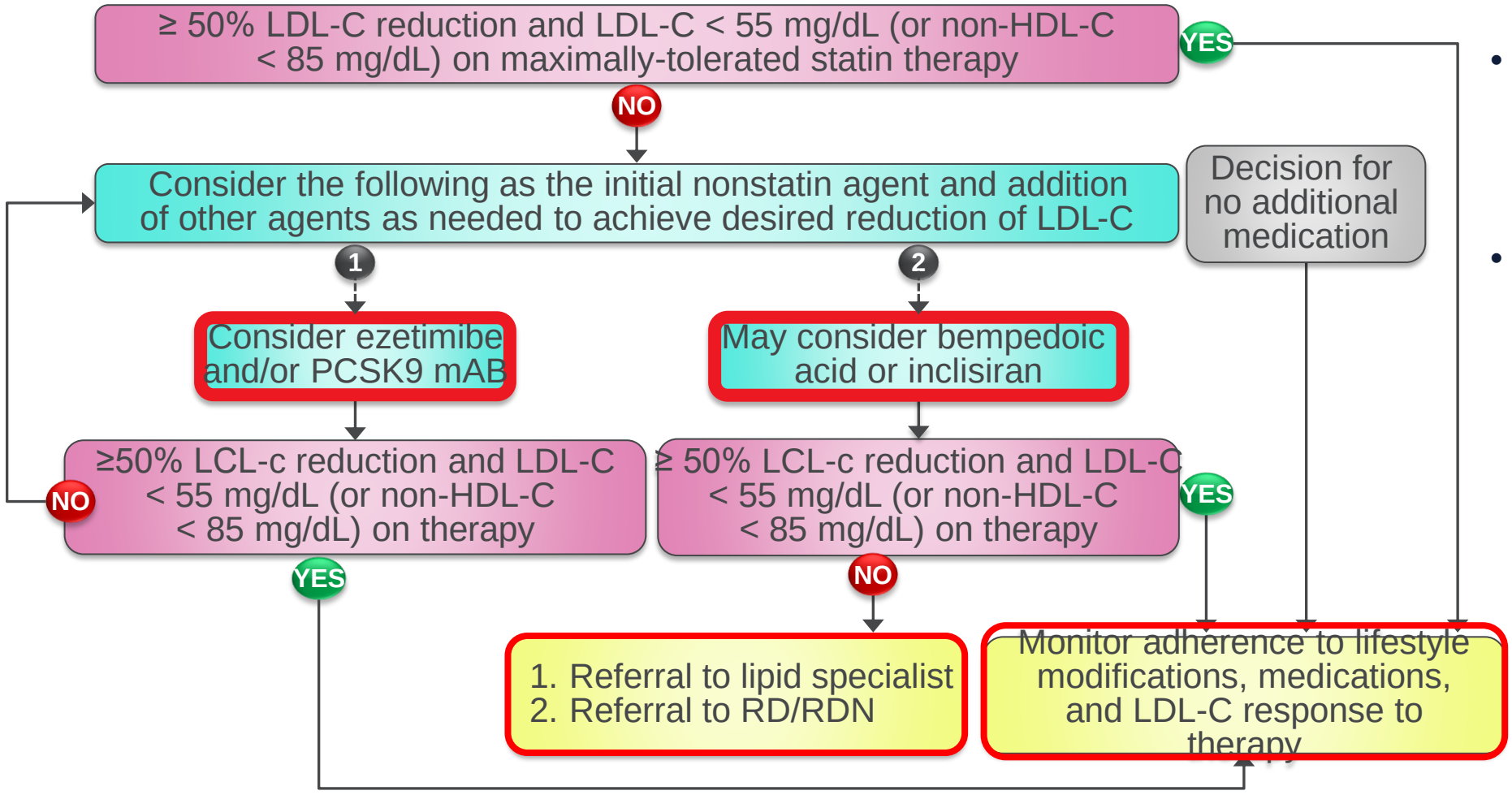
Lloyd-Jones DM et al. *J Am Coll Cardiol.* 2022 DOI: 10.1016/j.jacc.2022.07.006

Clinical ASCVD Not at Very High Risk, On Statin Therapy for Secondary Prevention



Lloyd-Jones D et al. *J Am Coll Cardiol.* 2022 Oct, 80 (14) 1366–1418.

Clinical ASCVD at Very High Risk, On Statin Therapy for Secondary Prevention



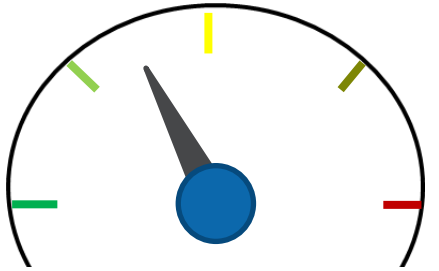
- **New LDL-C threshold: < 55 mg/dL for very high-risk ASCVD patients**
- To reach this threshold, combination therapy with maximally tolerated statin + another agent (PCSK9i or inclisiran or bempedoic acid) will be needed

Lloyd-Jones D et al. *J Am Coll Cardiol.* 2022 Oct, 80 (14) 1366–1418.

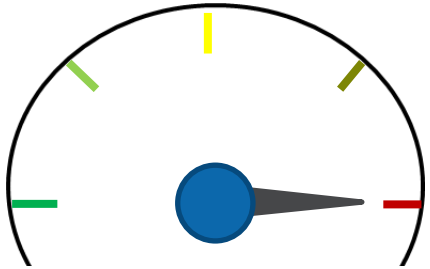
Statin Intolerance

- Statin nonadherence: Up to 20% of patients
  prescribed a statin stop it due to side effects
- GAUSS-3 study: Blinded, placebo-controlled
  statin rechallenge in patients with history of statin-associated muscle symptoms
  - 43% had statin intolerance
- PRIMO study: 7,924 patients on high-dose statins
  - 10.5% reported myalgias (38% with lifestyle-limiting side effects)

NLA 2022 Update: Statin Intolerance



Partial Intolerance:
Ability to tolerate a lower dose of statin than is required to achieve the desired therapeutic objective



Complete Intolerance:
Patient is unable to tolerate any statin dose or regimen

Finding a tolerable statin acceptable regimen may require modification of the statin, statin dose, and/or dosing regimen

Bruckert et al. *Cardiovasc Drugs Ther* 2005;19:403-14. Palapinyo S. Nissen S, *JAMA*. 2016;315:1580-1590.

https://www.lipid.org/nla/scientific-statement-statin-intolerance-new-definition-and-key-considerations-ascvd-risk

Screening for Atherosclerosis

Risk Factors vs Disease

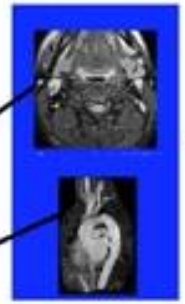
Numerous Risk Factors

- High LDL
- Low HDL
- High BP
- Diabetes
- Smoking
- CRP
- Metabolic Syn
- Lp(a)
- Homocysteine
- Dense LDL
- Lp-PLA2
- ApoB/ApoA
- Family History
- Sedentary Life
- Obesity
- Stress
- ...
- ?

Over 200 risk factors have been reported.

Examples of Arterial Structure Tests

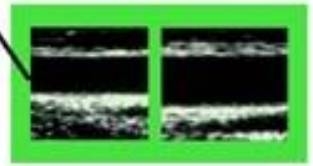
Carotid IMT and Plaque Measured by Ultrasound



Aortic and Carotid Plaque Detected by MRI

Coronary Calcium Score Measured by CT

Ankle Brachial Index

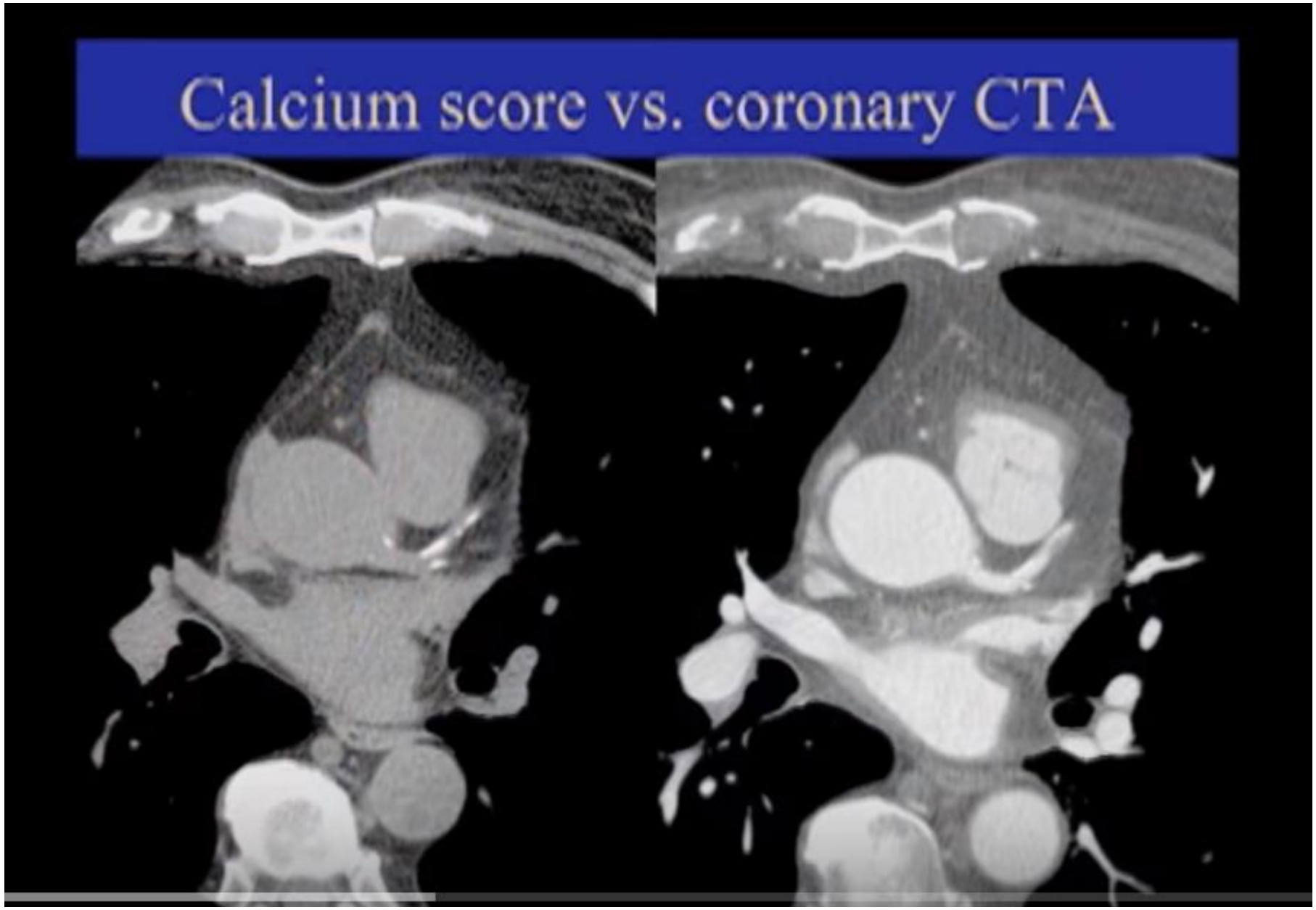


Brachial Vasoreactivity Measured by Ultrasound

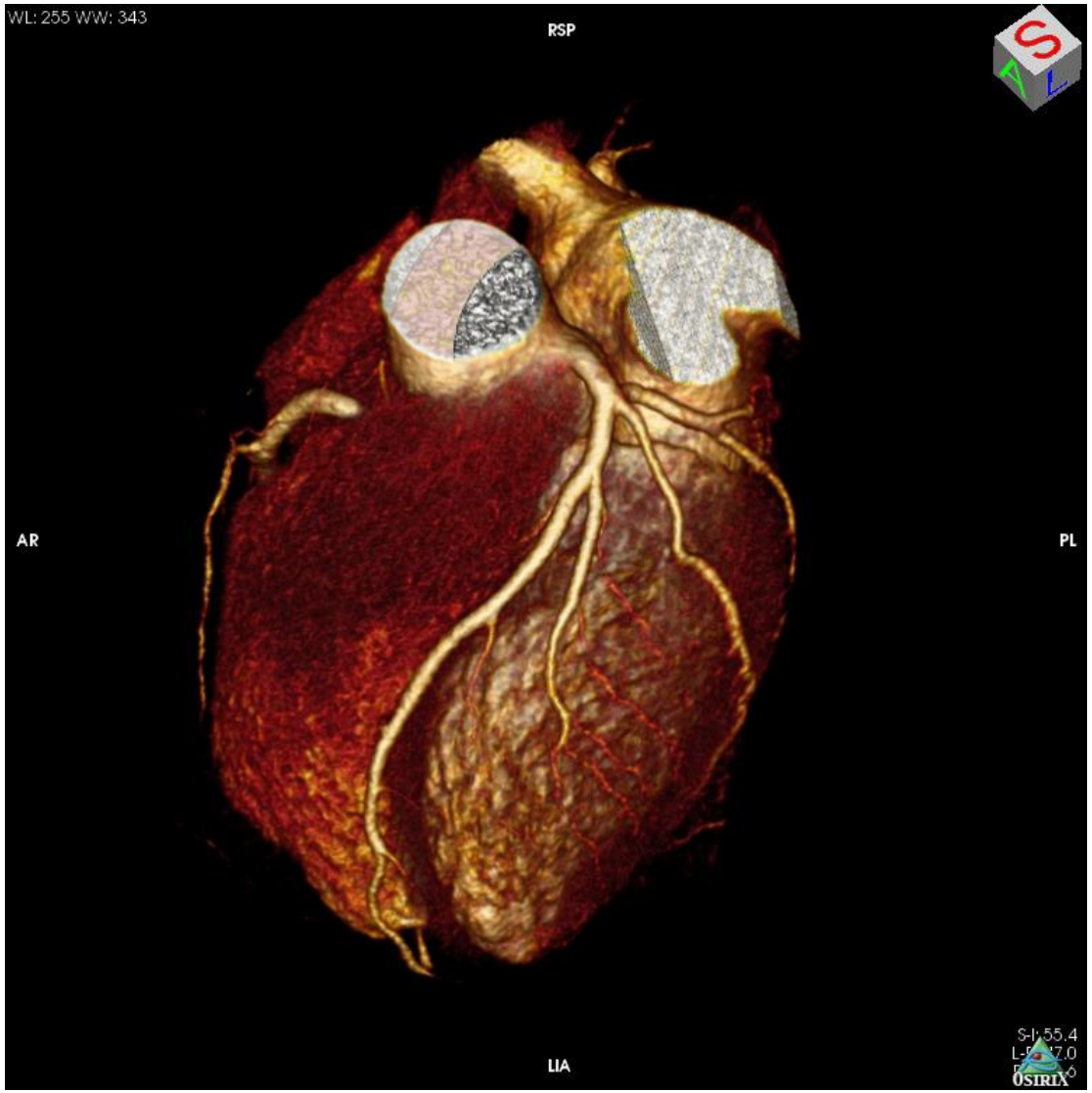
Vascular Compliance Measured by Radial Tonometry

Examples of Arterial Function Tests

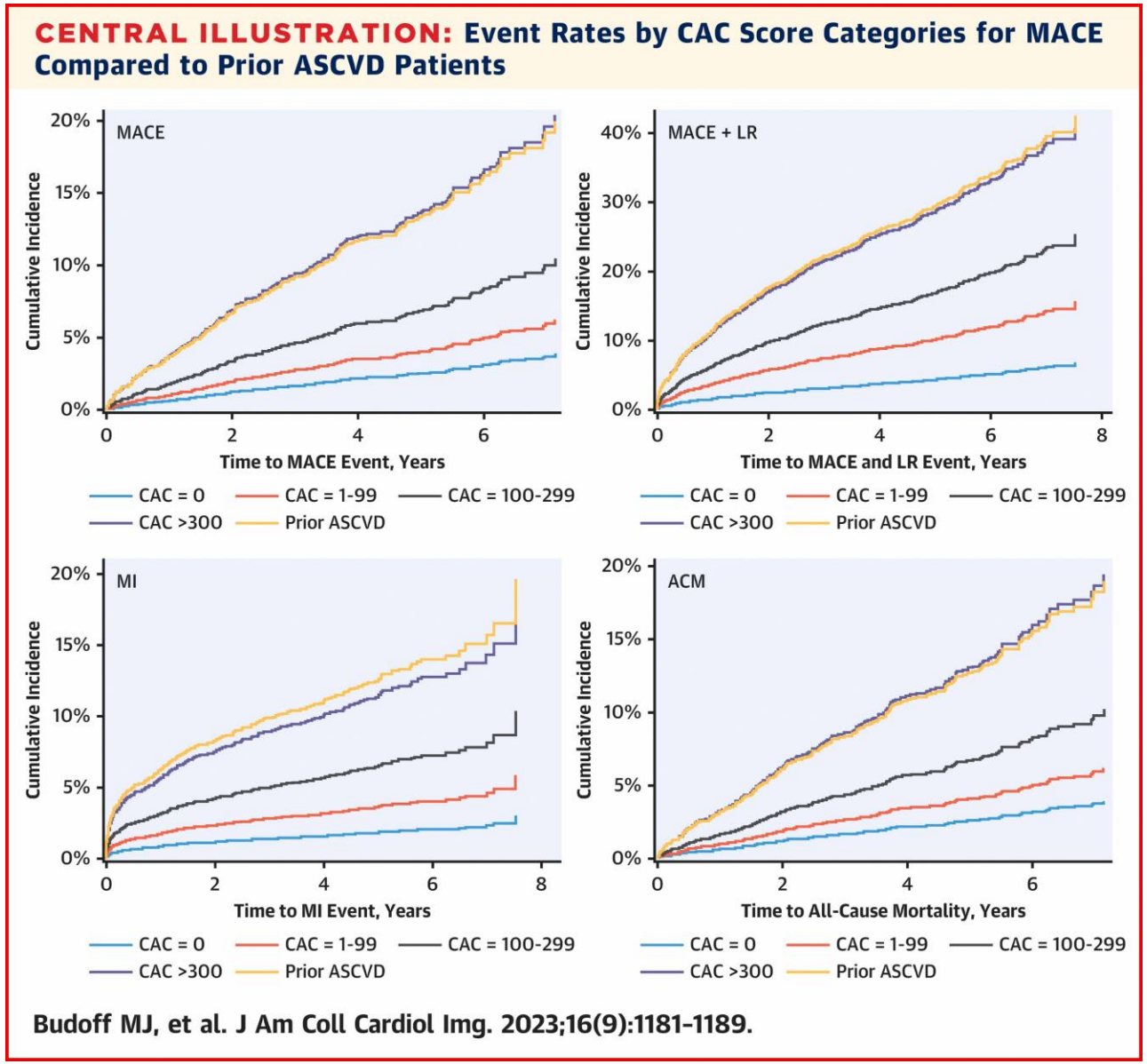
Microvascular Reactivity Measured by Fingertip Tonometry


Calcium score vs. coronary CTA

Coronary CT Angiography: Best Imaging Modality for Plaque Characterization



CAC Sore >300= Same Risk as Patients with ASCVD



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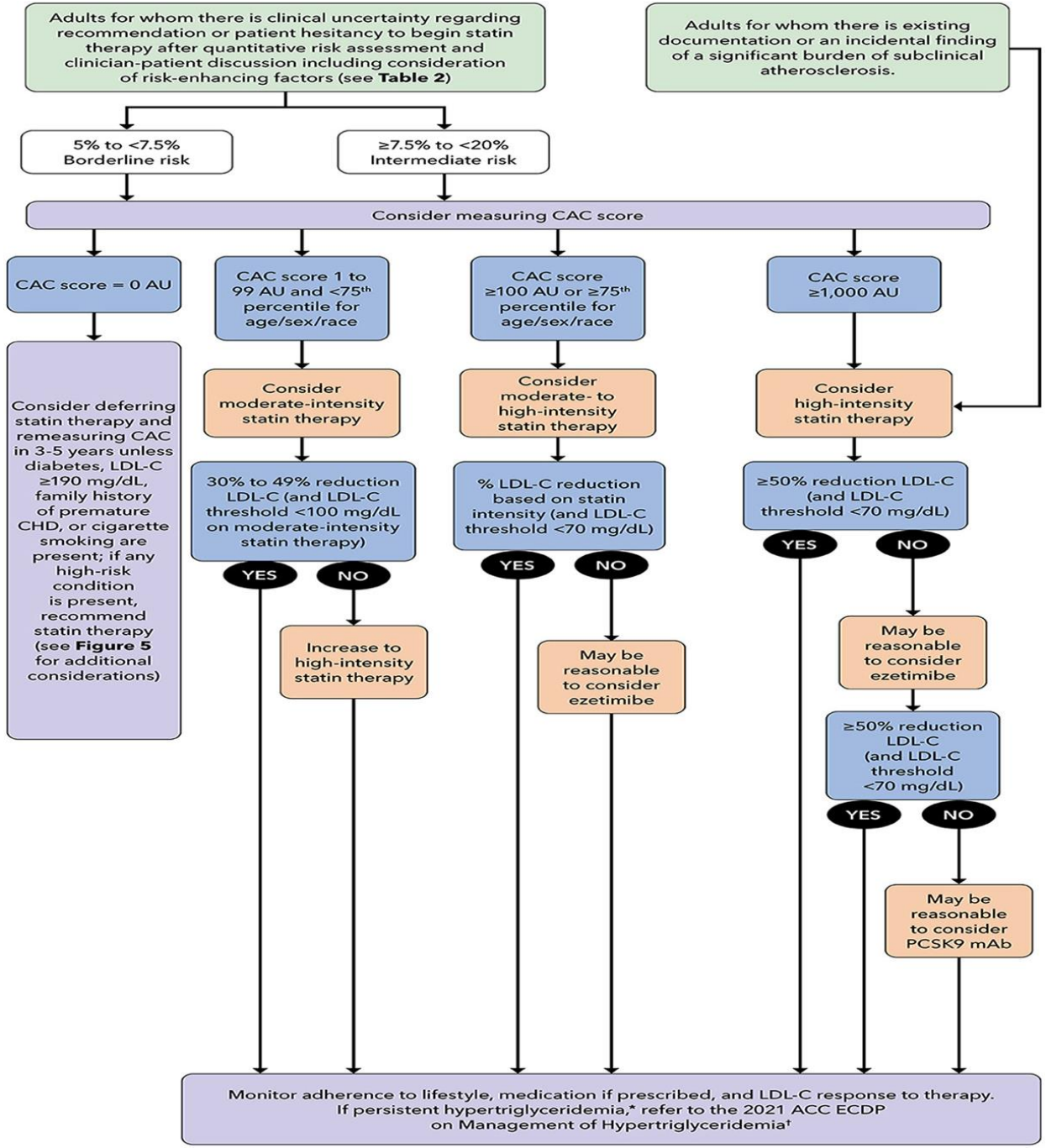

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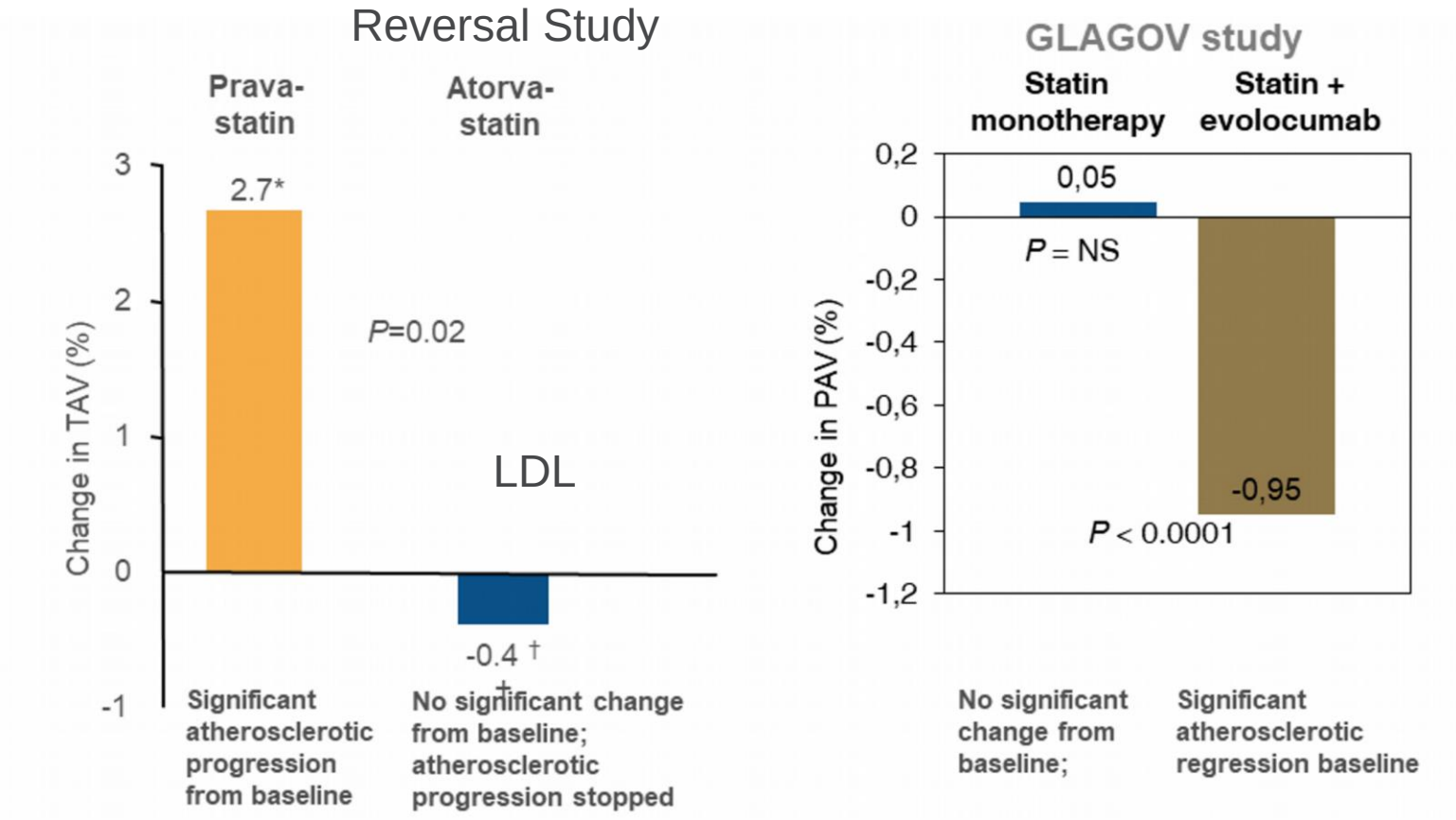
Audience Response Question

Based on the 2022 ACC Expert Consensus Statement, what is the recommended LDL-C treatment threshold for a patient with clinical ASCVD who is classified as very high risk?

a) < 35 mg/dL
b) < 55 mg/dL
c) < 70 mg/dL
d) <100 mg/dl

Plaque Stabilization versus Plaque Regression Depends on LDL Achieved



LDL of 36 or lower resulted in significant plaque regression

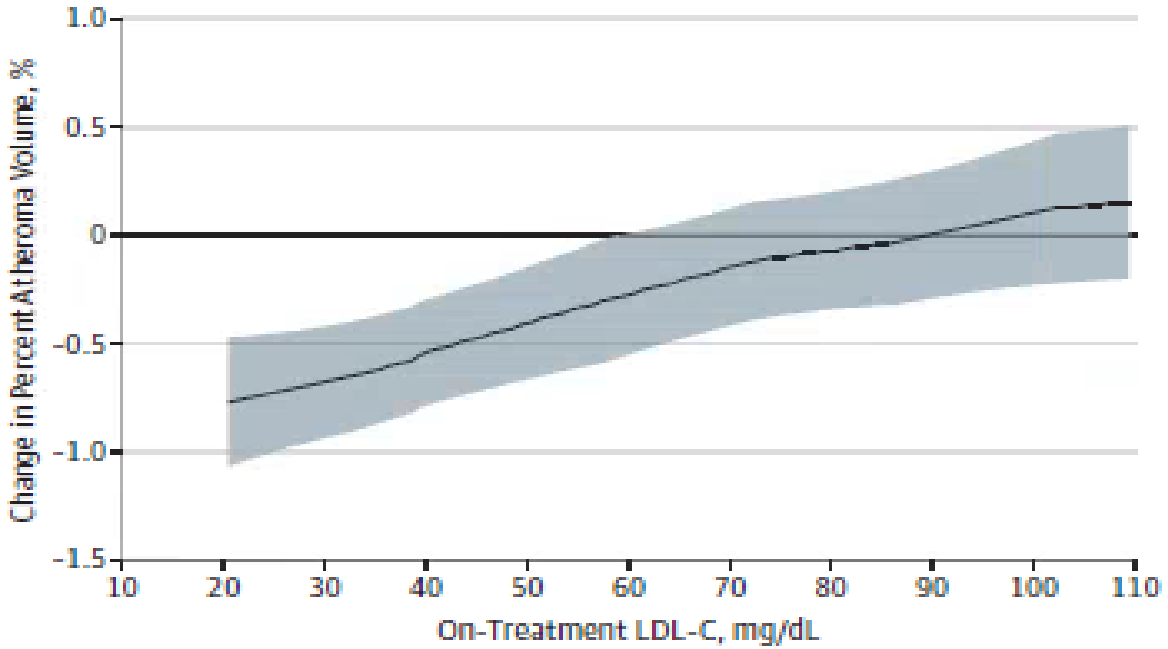
LDL in pravastatin group: 110
LDL in atorvastatin group: 79

LDL in statin group: 93
LDL in statin+PCSK9i group: 36

Nissen SE et al. JAMA 2004;291:1091-80.
Nicholls SJ et al. JAMA 2016;316:2373-2384.

GLAGOV Study: Benefit of LDL Lowering on Plaque Regression

Figure 4. Post Hoc Analysis Examining the Relationship Between Achieved LDL-C Level and Change in Percent Atheroma Volume



Local regression (LOESS) curve illustrating the post hoc analysis of the association (with 95% confidence intervals) between achieved low-density lipoprotein cholesterol (LDL-C) levels and the change in percent atheroma volume in all patients undergoing serial IVUS evaluation. Curve truncated at 20 and 110 mg/dL owing to the small number of values outside that range. To convert LDL-C values to mmol/L, multiply by 0.0259.

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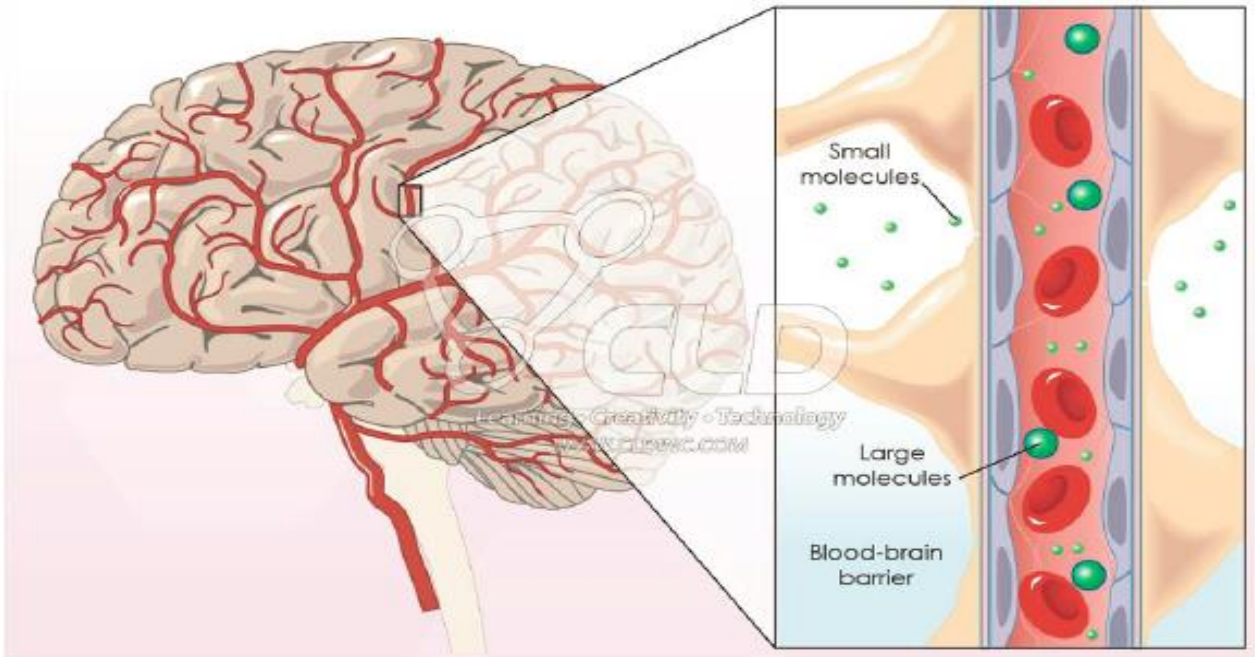
JAMA. 2016;316(22):2373-2384

Cognition and PCSK9 Inhibitors

Brain synthesizes cholesterol locally



mAb (e.g., evolocumab) are too large to cross the intact blood-brain barrier

Nevertheless meta-analysis* of adverse events from 6 trials in 9581 pts suggested an increased risk with PCSK9 inhibitors: HR 2.3 [1.1, 4.9]

- Event rates low (<1%)
- Unadjudicated, diverse AE terms reported
- Not correlated with LDL-C achieved

*Lipinski MJ, et al. *Eur Heart J.* 2016;37(6):536-545.

Conclusions

In patients with known cardiovascular disease on background statin followed for 20 months

1. **No differences btw evolocumab vs placebo**
   A. A battery of cognitive tests
   B. Patient-reported everyday cognition
   C. Adverse cognitive events reported by MD

2. **No evidence of differences in cognitive tests by achieved nadir LDL-C, even <25 mg/dL**

CENTRAL ILLUSTRATION: Coronary Atherosclerotic Plaque Regression

Imaging Plaque

Invasive

IVUS
Gold standard for plaque quantification, can assess morphology with post-processing

OCT
Higher resolution allows visualization of thin cap fibroatheroma and lipid content

NIRS
Semiquantitative lipid measurement

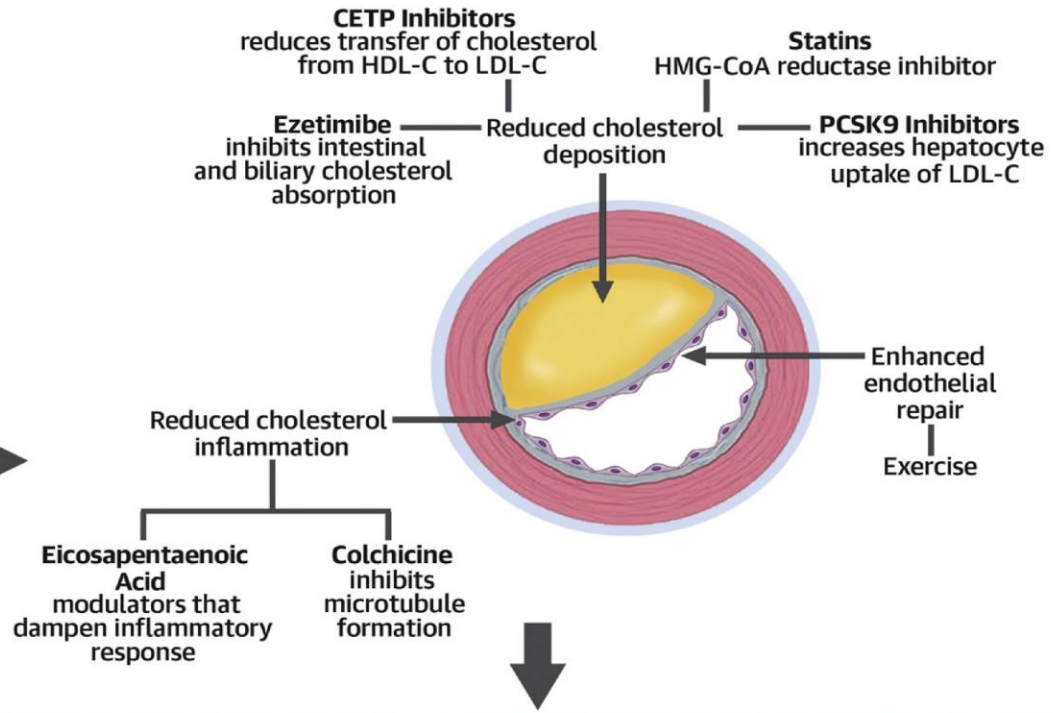
Non-Invasive

CCTA
Can measure volume and characterize plaque, assess high risk features, good correlation with IVUS

PET
In development, emerging molecular imaging probes

MRI
Some success in carotid imaging, ongoing studies to determine use for coronary assessment

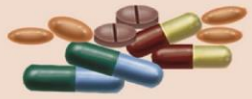
Plaque Regression Strategies



Potential Future Applications

Further outcome and therapeutic trials

Direct imaging to monitor treatment response



Population screening

Dawson, L.P. et al. J Am Coll Cardiol. 2022;79(1):66-82.

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Conclusions

- Most high-risk ASCVD patients are not at LDL-C goal
- Combination therapy with statin and non statin agents are needed to achieve LDL goals
- Patients with elevated CAC score >300 should be considered secondary prevention
- Utilize coronary calcium score to get high risk patients access to non-statin agents
- Get the LDL as low as you can for secondary prevention

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CARDIOVASCULAR CENTER

The Treatment Landscape for LDL-C Lowering: 2023 and Beyond

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Disclosures

- Local PI (Esperion, CLEAR Outcomes)

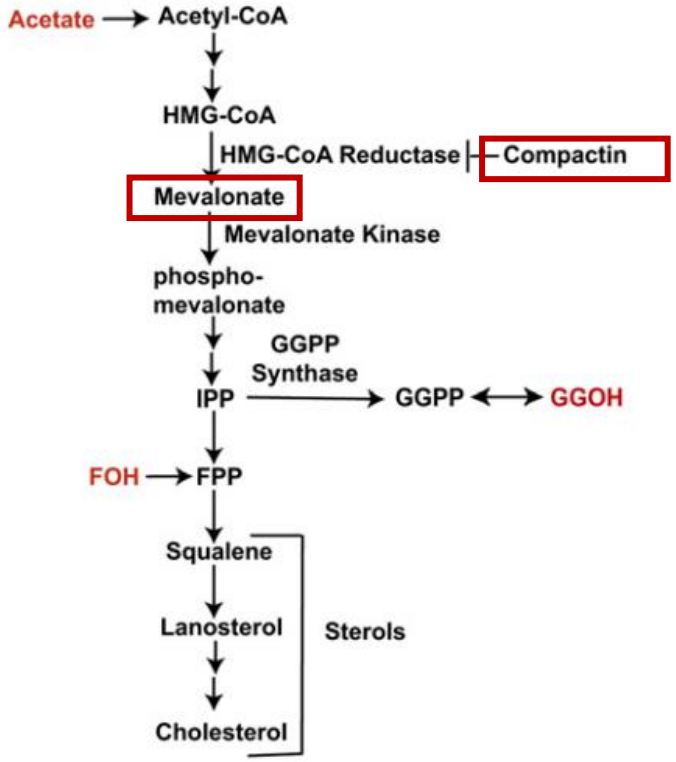
1987

The Birth of Statins

- Mevastatin/compactin first used to treat patient with HoFH in 1977
  - Lowered LDL-C from 1000 mg/dl to 700 mg/dL
  - Associated with possible toxicity at higher doses in animals (lymphoma)—development discontinued
- Merck subsequently identified lovastatin from another fungus
  - Lovastatin—1st statin to reach commercial availability in 1987

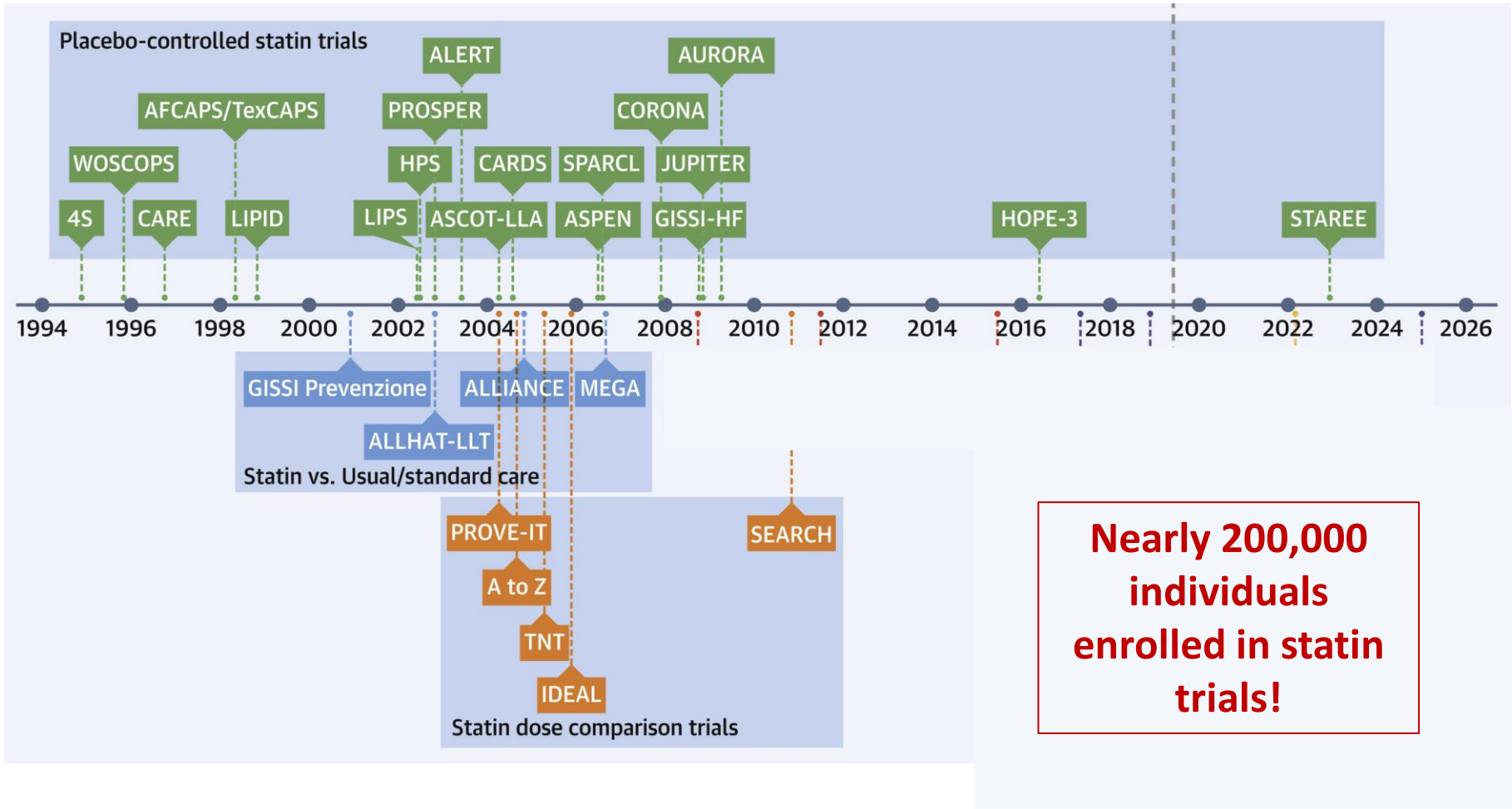
Akira Endo

Figure 3 Akira Yamamoto's homozygous patient with familial hypercholesterolemia who first received compactin in 1978. Her treatment paved the way to the clinical development of compactin. Here she is holding her baby 7 years after the treatment.



Nature Medicine. 2008;14:1050-52

Timeline of Completed and Ongoing LDL Cholesterol–Lowering Cardiovascular Outcome Trials



Nearly 200,000 individuals enrolled in statin trials!

Lovastatin: 1987

Simvastatin: 1991

Pravastatin: 1991

Atorvastatin: 1996

Cerivastatin: 1997

Withdrawn: 2001

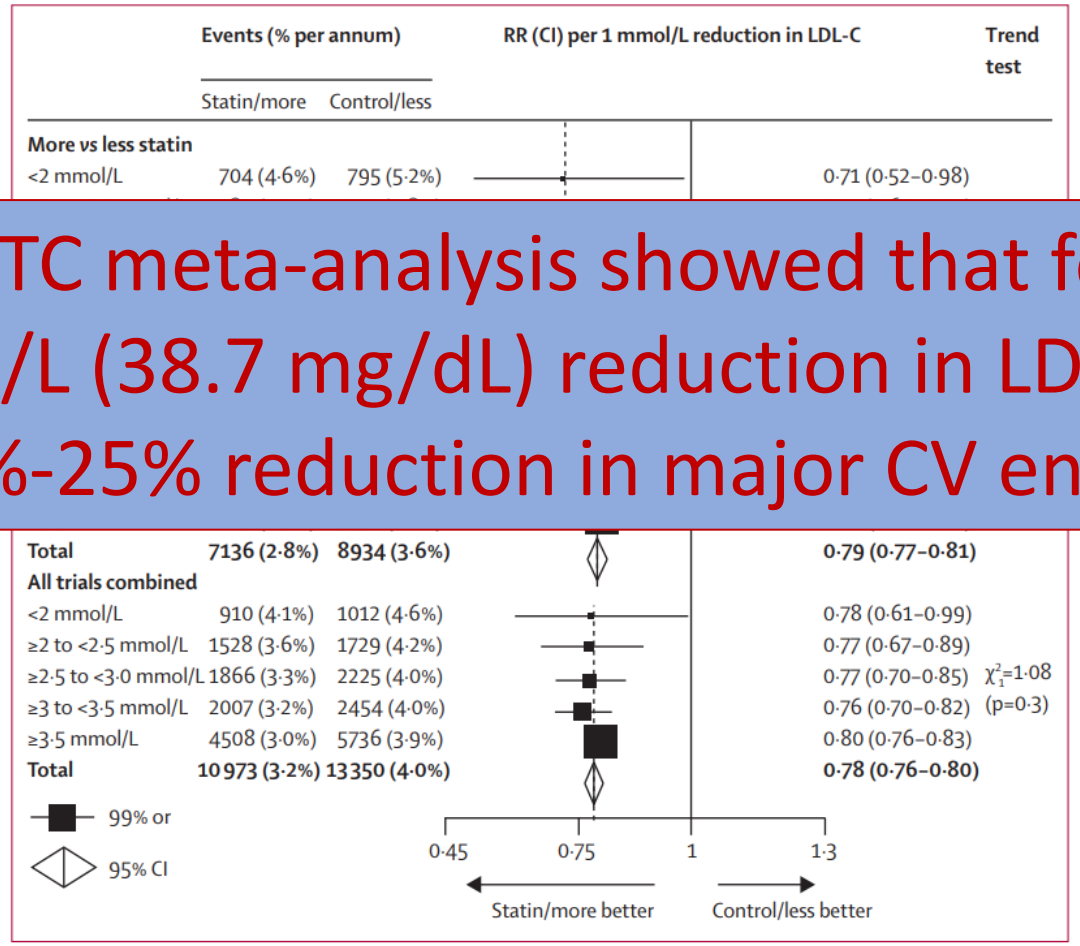
Fluvastatin: 2000

Rosuvastatin: 2003

Pitavastatin: 2009

J Am Coll Cardiol 2020;75:1945–55

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomized trials

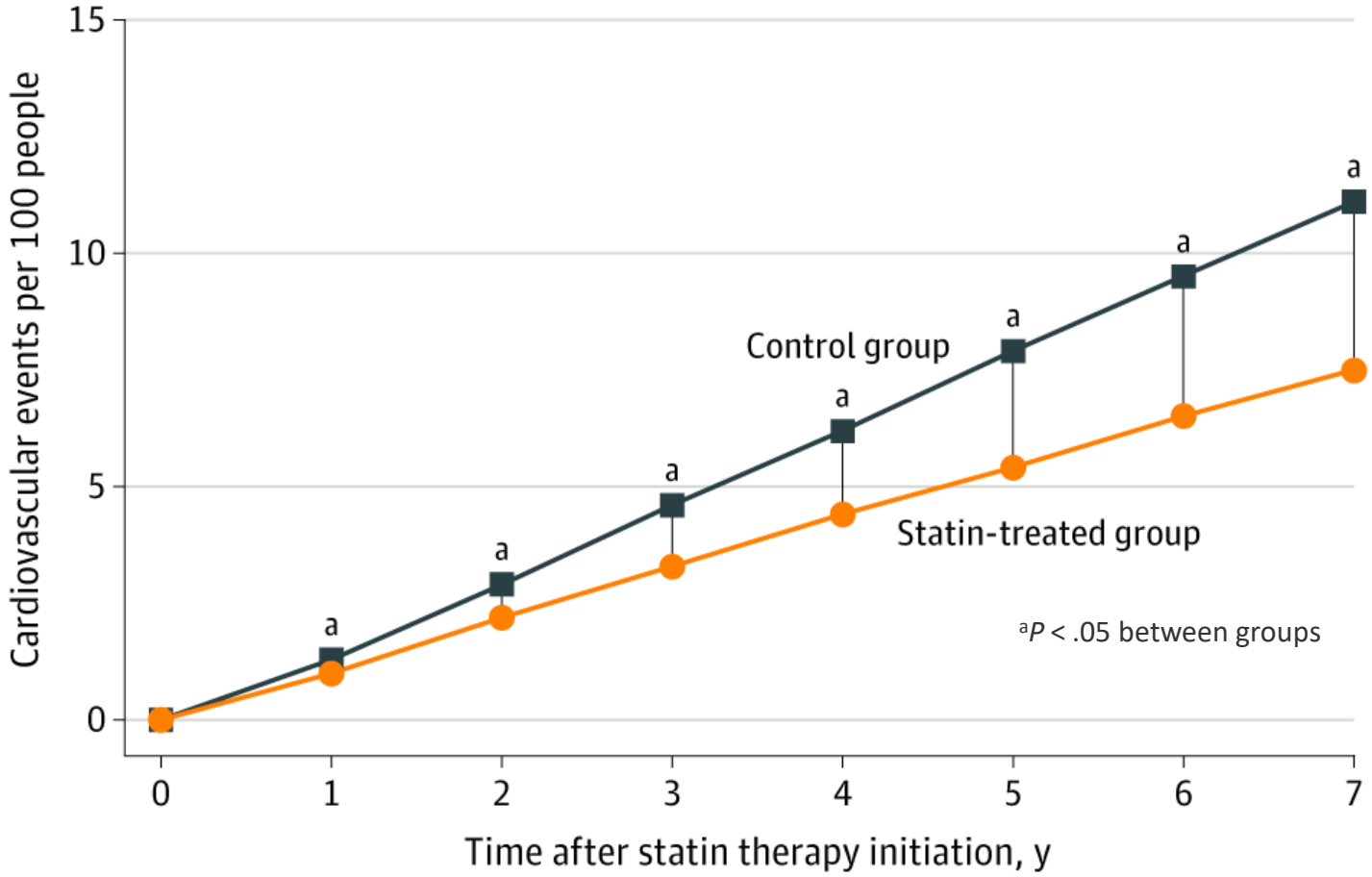


CTTC meta-analysis showed that for every 1 mmol/L (38.7 mg/dL) reduction in LDL-C there is a 20%-25% reduction in major CV end points.

Figure 4: Effects on major vascular events per 1·0 mmol/L reduction in LDL cholesterol, by baseline LDL cholesterol concentration on the less intensive or control regimen

Lancet 2010; 376: 1670–81

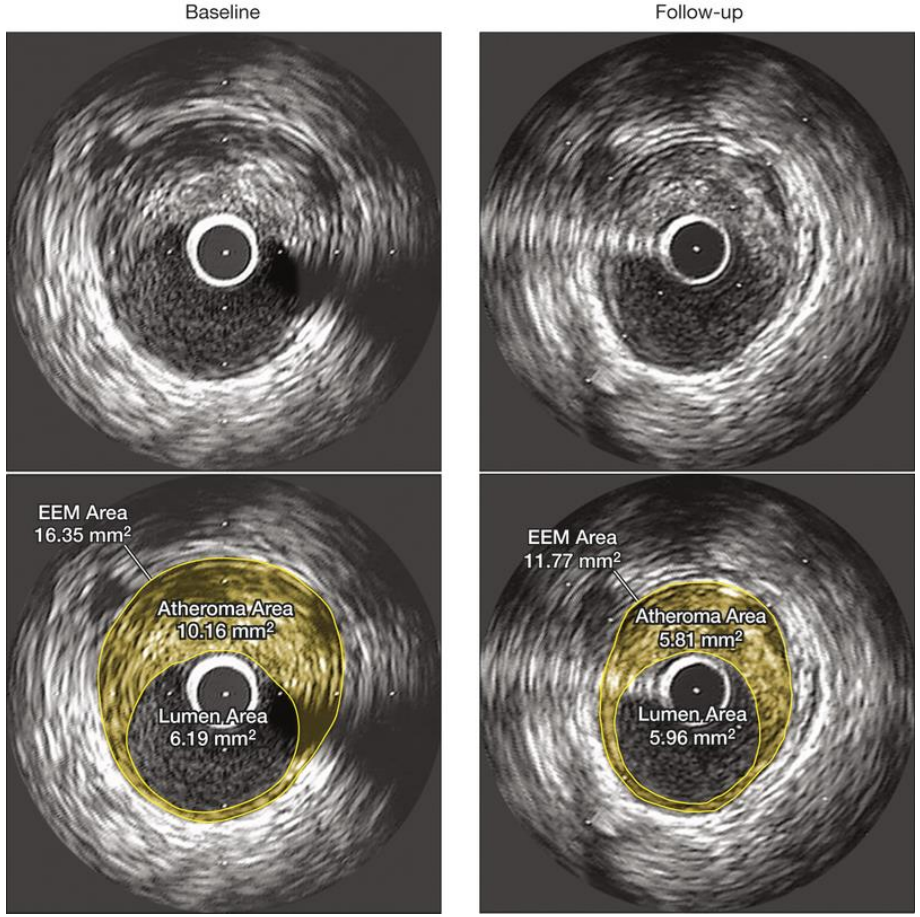
Evaluation of Time to Benefit of Statins for the Primary Prevention of Cardiovascular Events in Adults Aged 50 to 75 Years
A Meta-analysis



Benefits of statin therapy increase steadily with longer follow-up

JAMA Intern Med. 2021;181(2):179-185.

Effect of Very High-Intensity Statin Therapy on Regression of Coronary Atherosclerosis: The ASTEROID Trial



- To assess whether *very intensive statin therapy* could *regress* coronary atherosclerosis as determined by IVUS imaging.
- 349 patients underwent IVUS examination and received rosuvastatin 40 mg over 24 months

  Baseline LDL-C level of **130.4** (34.3) mg/dL declined to **60.8** (20.0) mg/dL, a mean reduction of 53.2% (P<.001).

Significant reductions in

PAV for the entire vessel

Atheroma volume in the most diseased

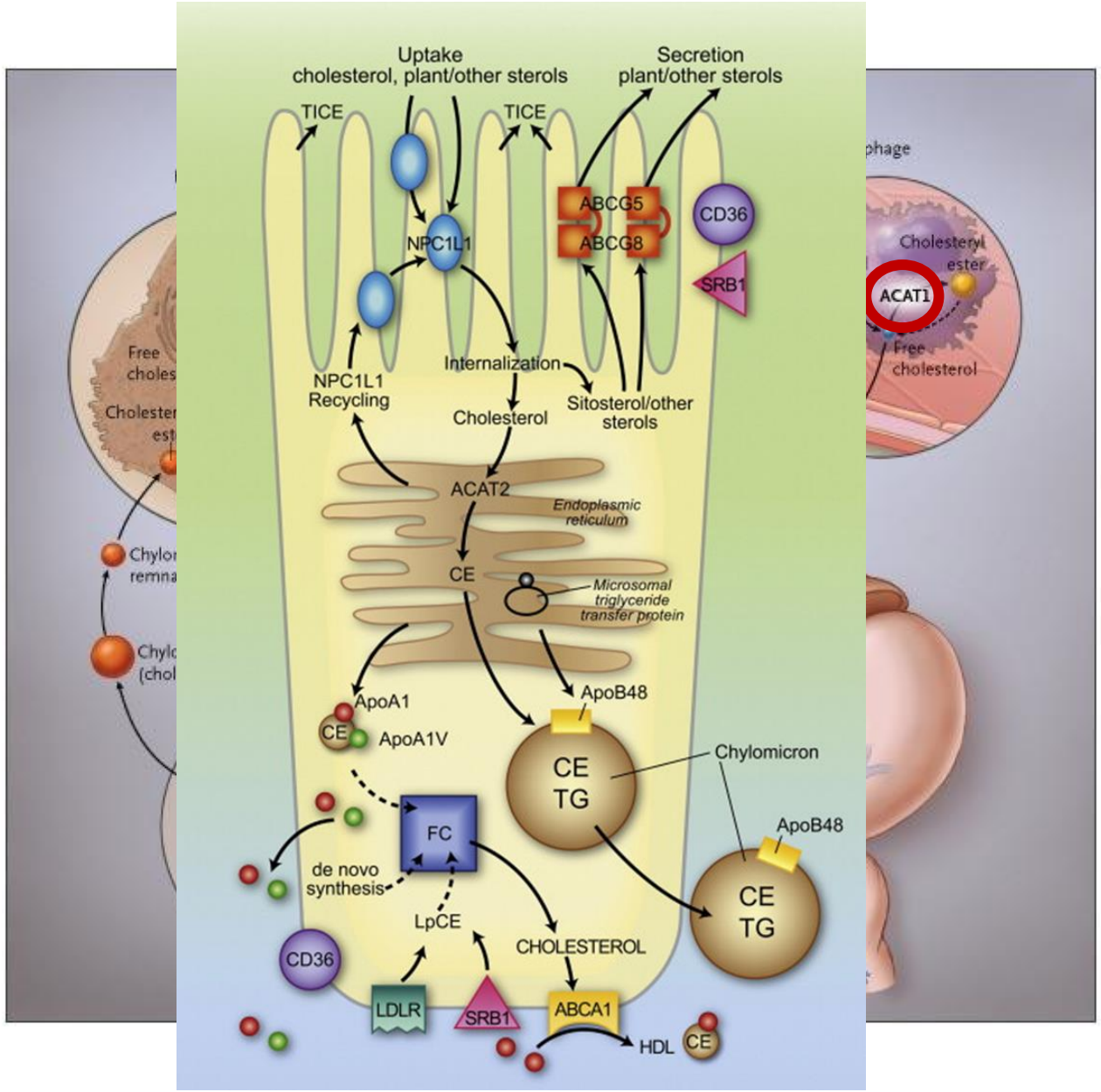
Total atheroma volume

JAMA. 2006 Apr 5;295(13):1556-65

2002

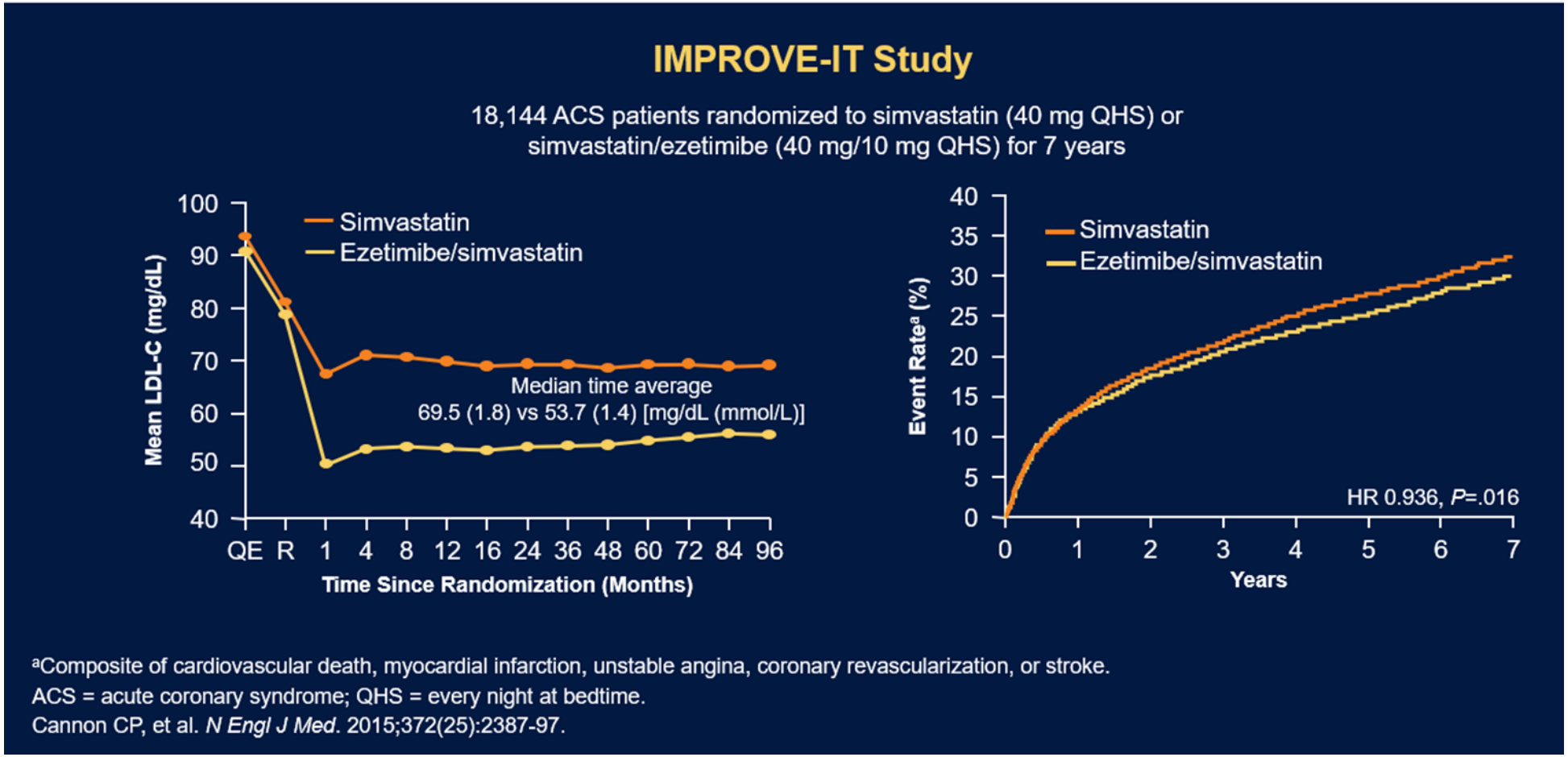
Ezetimibe

- Discovered as part of program to identify ACAT inhibitors for lipid lowering
  - Catalyzes formation CE from cholesterol and long-chain fatty-acid-acyl CoA to store and transport cholesterol
- Weak ACAT inhibitor, but lowered cholesterol
  - Different mechanism?
- At time of FDA approval in 2002, target not known
  - Inhibits NPC1L1 transporter



N Engl J Med 2006; 354:1253-1263

Timeline of Completed and Ongoing LDL-C Lowering Cardiovascular Outcome Trials



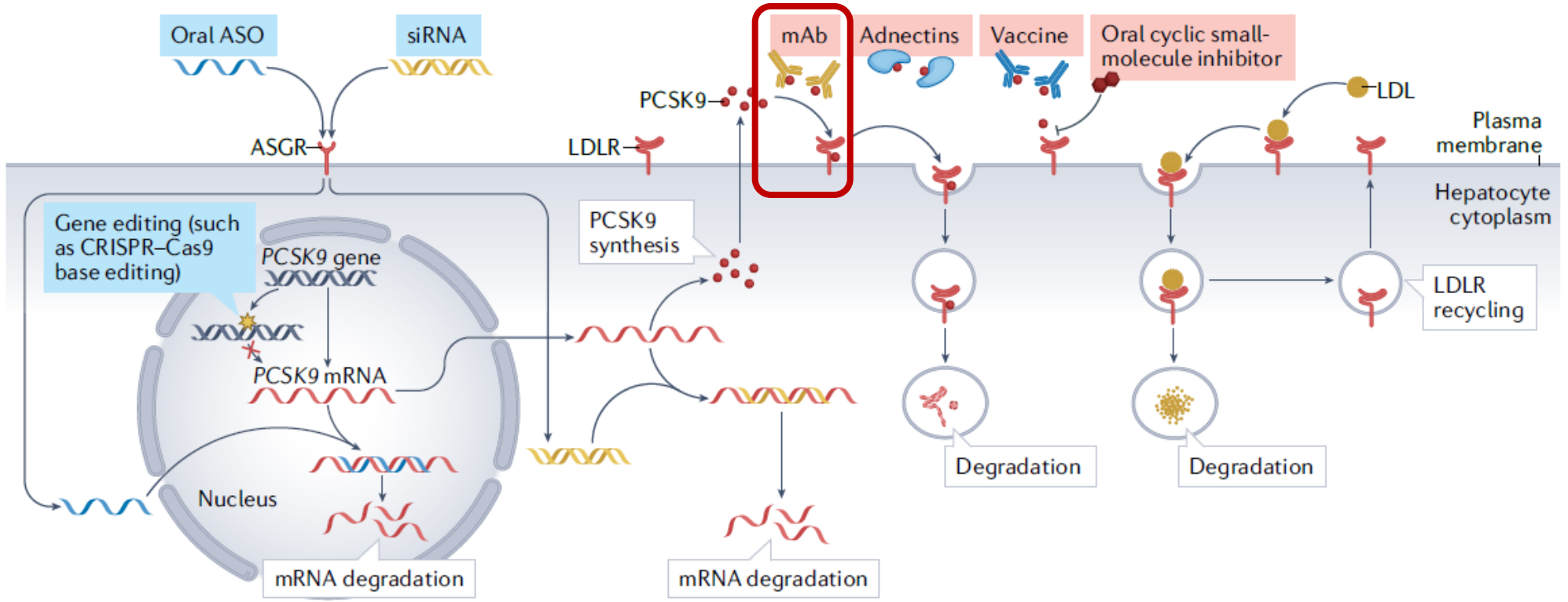
[a]Composite of cardiovascular death, myocardial infarction, unstable angina, coronary revascularization, or stroke.
ACS = acute coronary syndrome; QHS = every night at bedtime.
Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-97.

J Am Coll Cardiol 2020;75:1945–55

PCSK9-targeted interventions

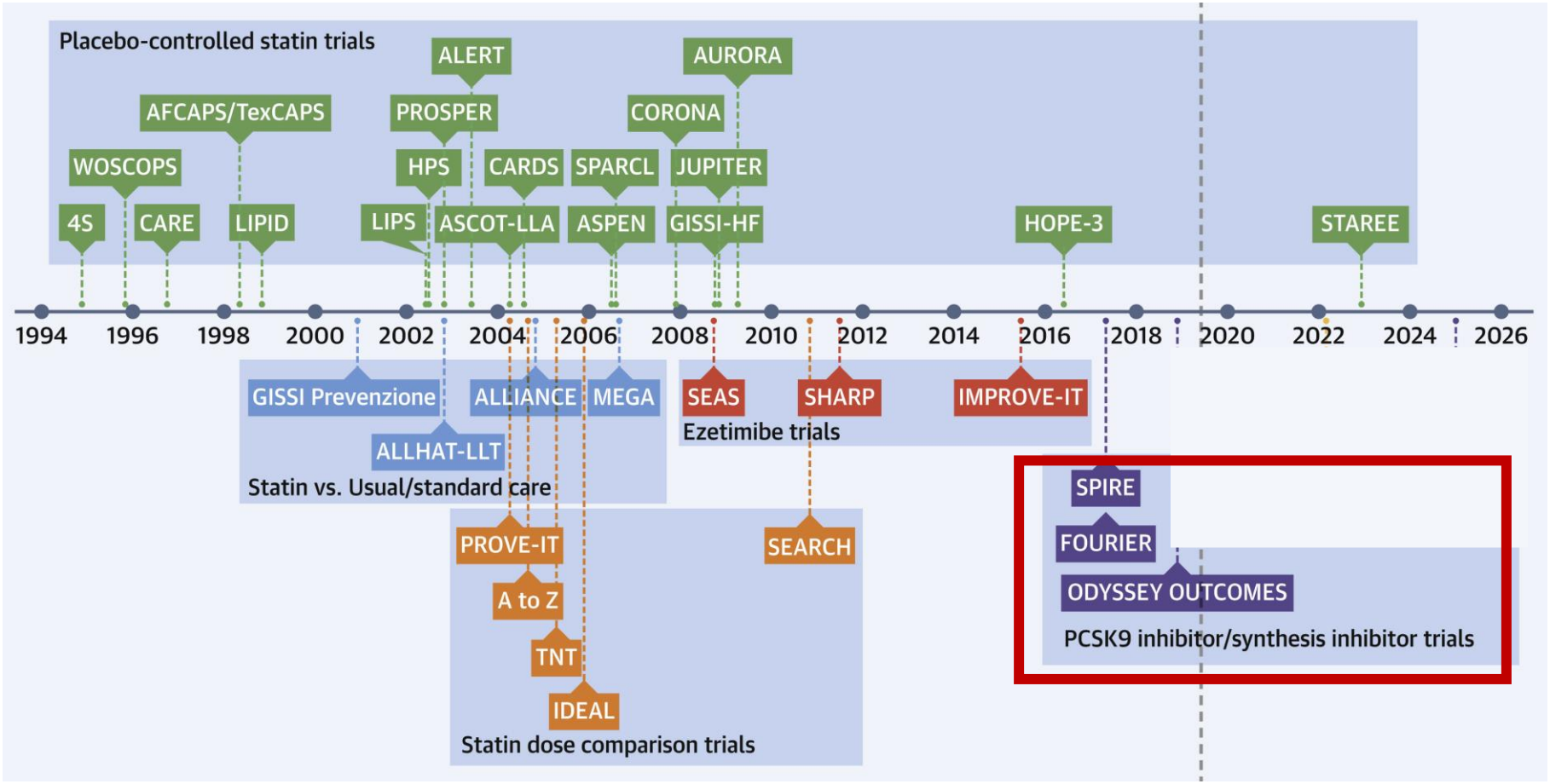
2015

- Bind PCSK9 to prevent targeted breakdown of LDL-R in lysozymes



Nature Rev Cardiol.2021;18;805-6

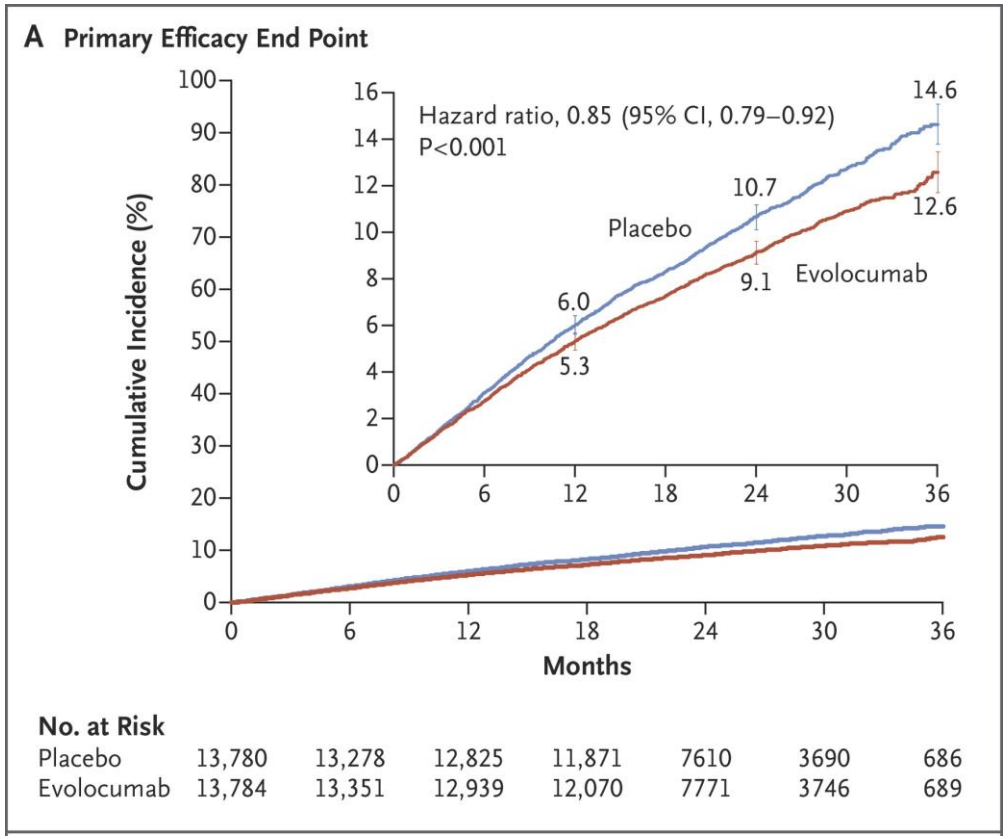
Timeline of Completed and Ongoing LDL Cholesterol–Lowering Cardiovascular Outcome Trials



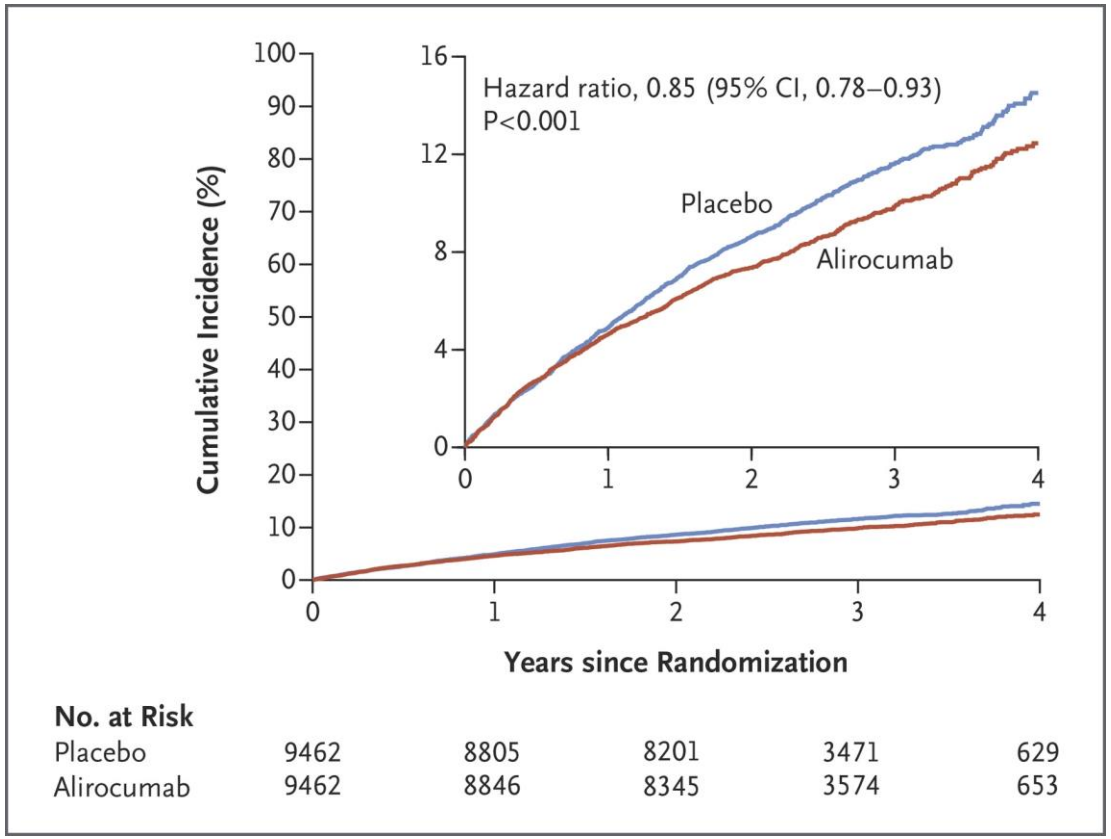
J Am Coll Cardiol 2020;75:1945–55

PCKS9 mAb CV Outcomes Trials

FOURIER

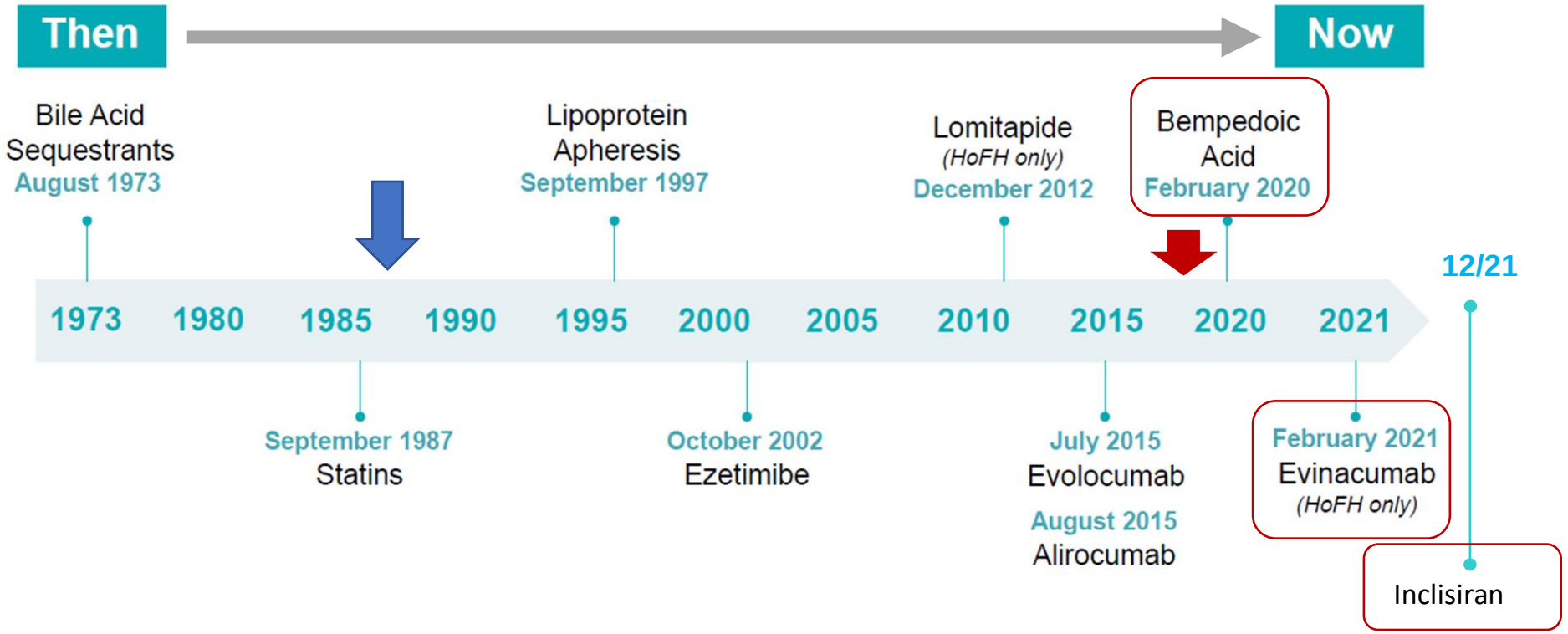


ODYSSEY Outcomes



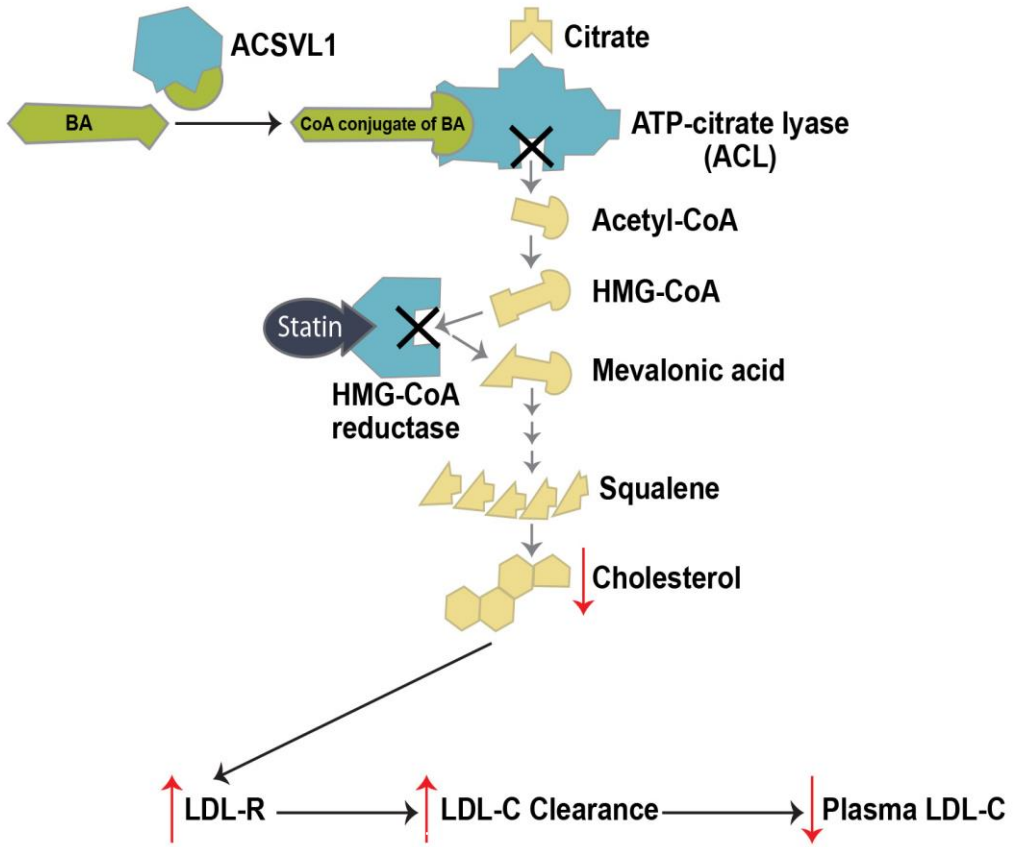
N Engl J Med. 2017;376(16):1527-39;
N Engl J Med 2018; 379:2097-2107

The LDL-C Treatment Journey…



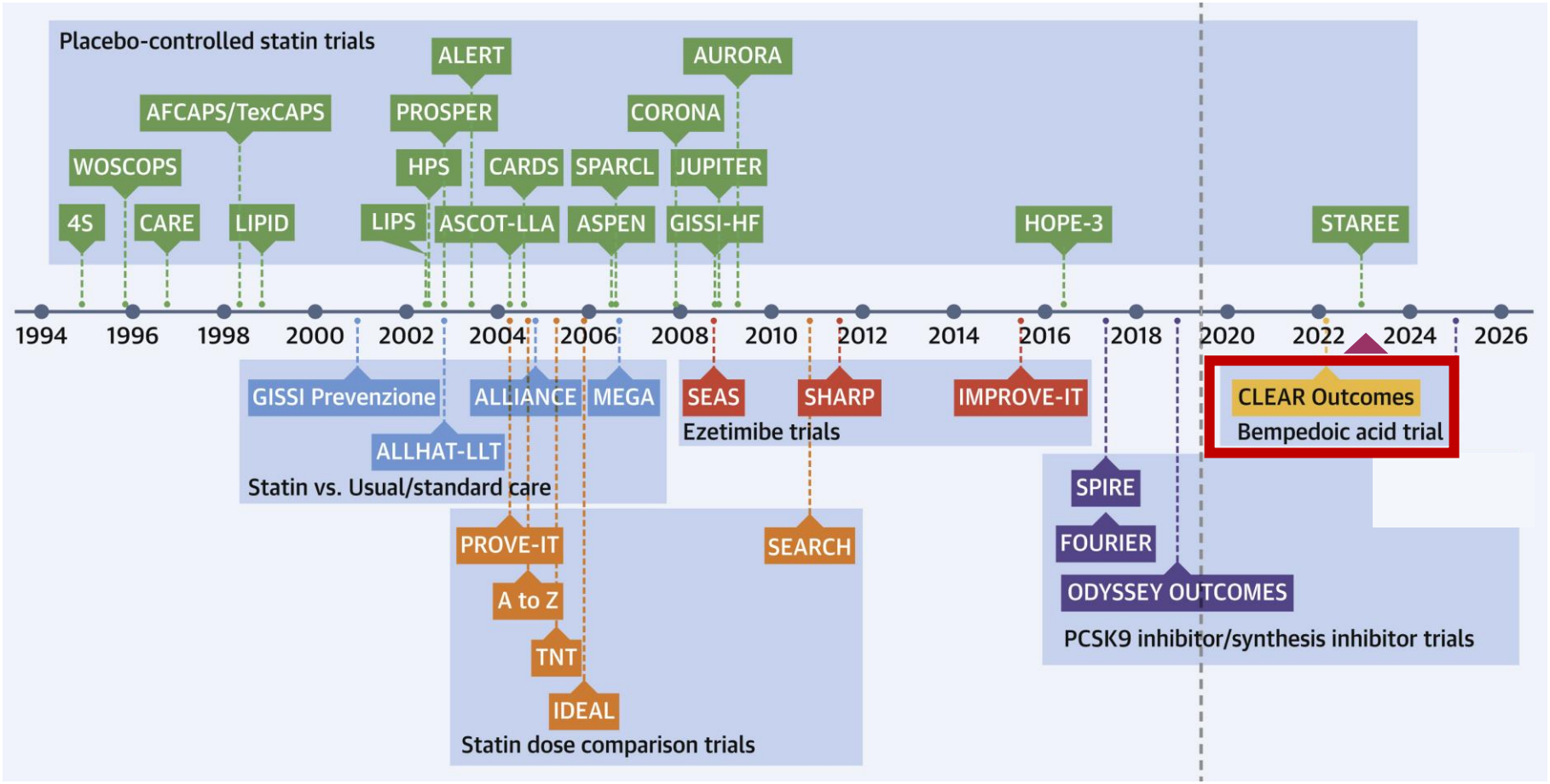
2/2020

Bempedoic Acid Mechanism of Action



- Bempedoic acid is a prodrug activated in liver by very-long-chain acyl-CoA synthetase-1 (ACSVL1)
- Activated bempedoic acid acts in same cholesterol synthesis pathway as statins
  - Inhibits ATP-citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase
- Activated bempedoic acid is ***not*** present in skeletal muscle
- LDL-C lowering
  - ~15-17% when added to statin
  - ~24% as monotherapy

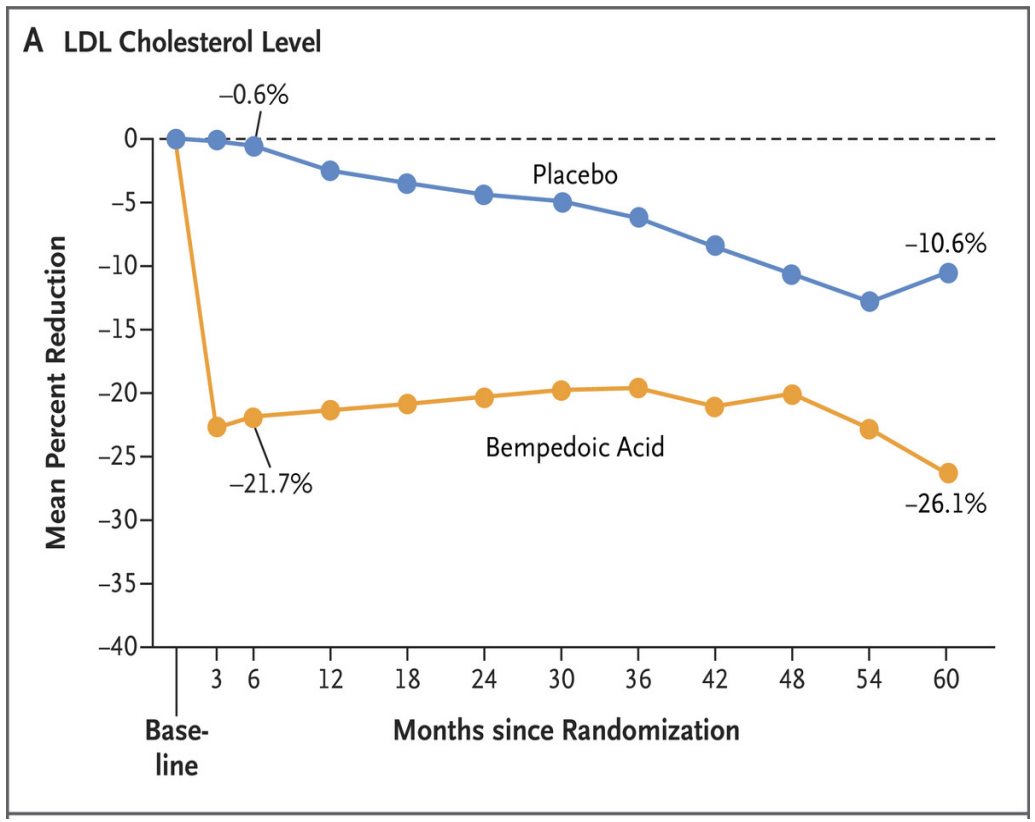
Timeline of Completed and Ongoing LDL Cholesterol–Lowering Cardiovascular Outcome Trials

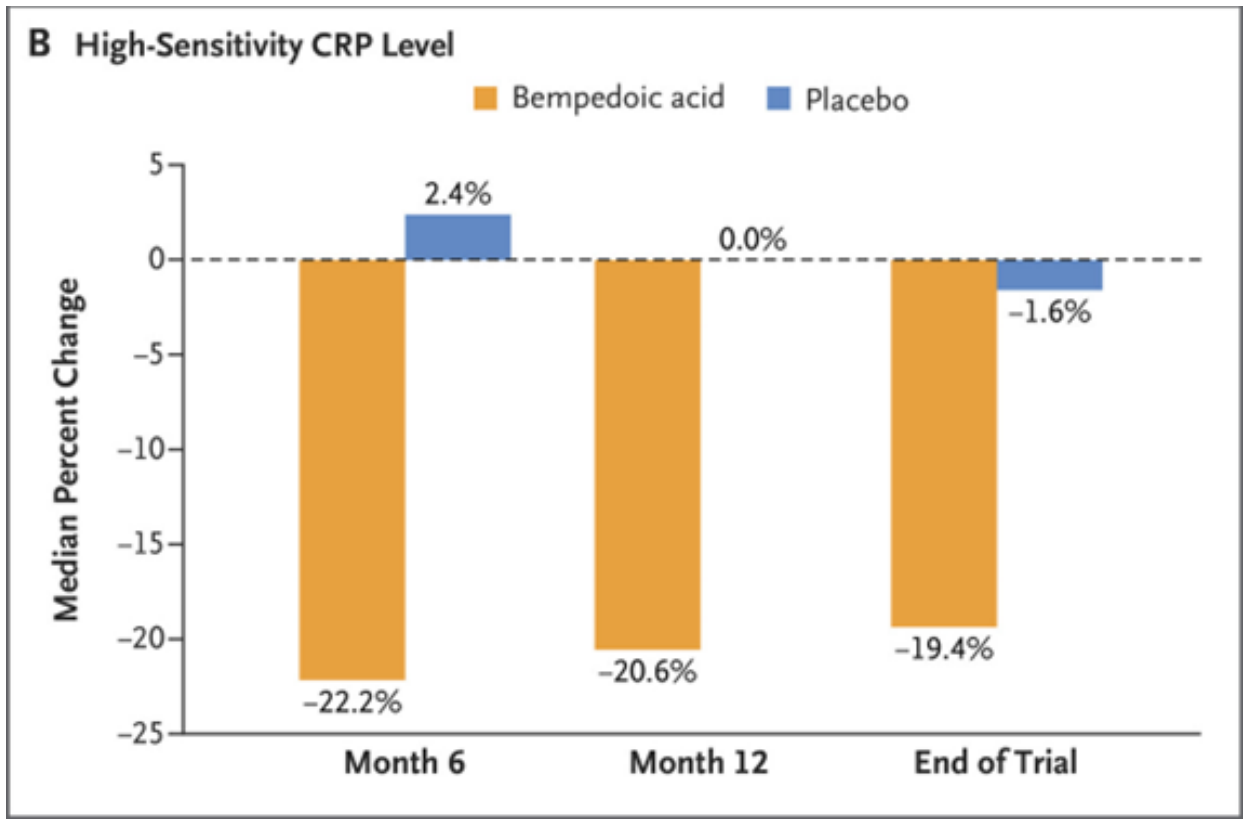


J Am Coll Cardiol 2020;75:1945–55

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

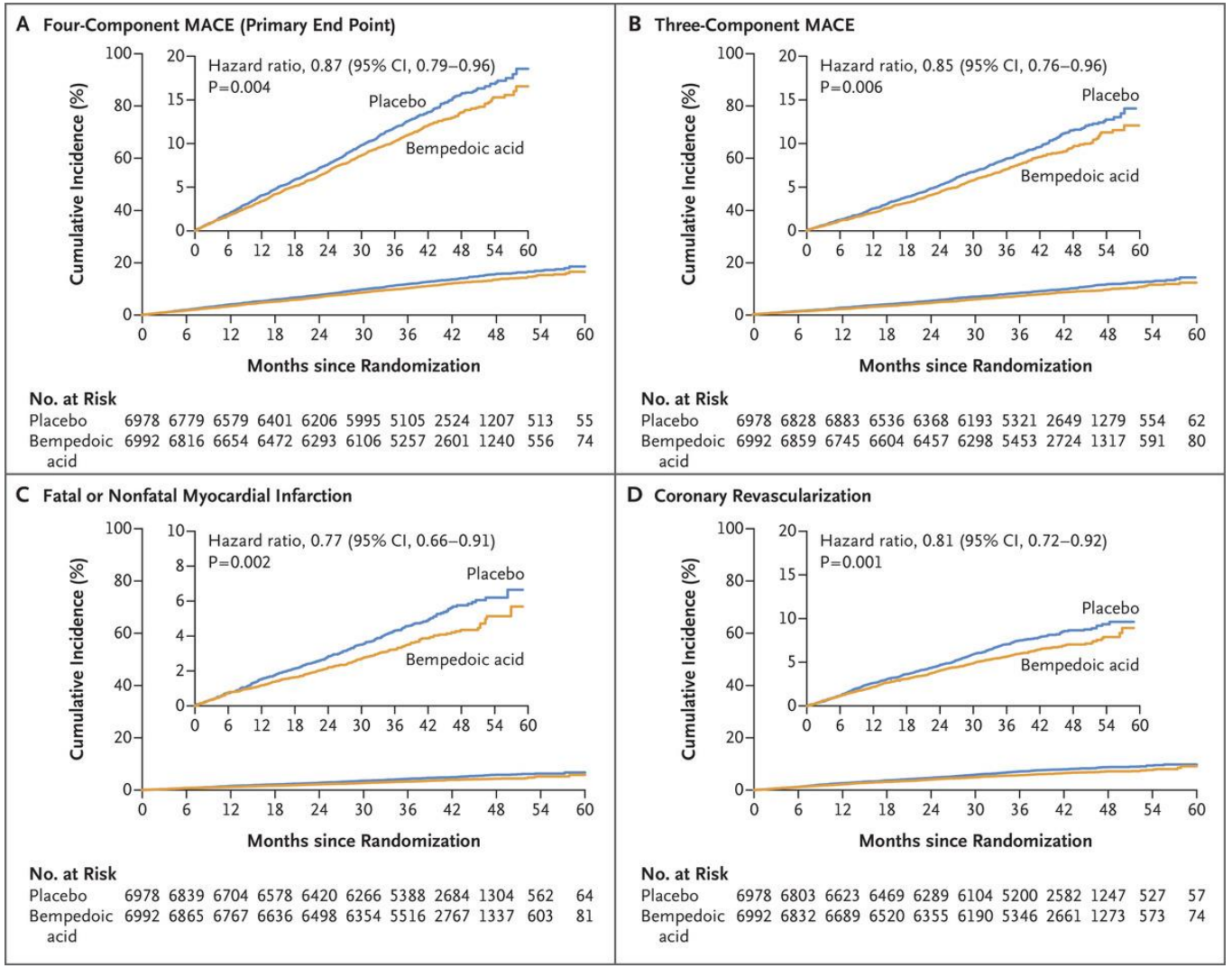
Steven E. Nissen, M.D., A. Michael Lincoff, M.D., Danielle Brennan, M.S., Kausik K. Ray, M.D., Denise Mason, B.S.N., John J.P. Kastelein, M.D., Paul D. Thompson, M.D., Peter Libby, M.D., Leslie Cho, M.D., Jorge Plutzky, M.D., Harold E. Bays, M.D., Patrick M. Moriarty, M.D., et al., for the CLEAR Outcomes Investigators*





N Engl J Med 2023.
DOI: 10.1056/NEJMoa2215024

Cumulative Incidence of CV Events



N Engl J Med 2023.
DOI: 10.1056/NEJMoa2215024

CLEAR Outcomes: Primary Prevention Cohort

JAMA®

QUESTION In statin-intolerant primary prevention patients at high cardiovascular risk, does bempedoic acid reduce major adverse cardiovascular events?

CONCLUSION Treatment with bempedoic acid in primary prevention patients has the potential to reduce major adverse cardiovascular events.

POPULATION

2481 Women
1725 Men

Statin-intolerant adults without a prior cardiovascular event

Mean age: 68 years

LOCATIONS

1250 Centers worldwide

INTERVENTION

Total N = 13,970

4206 Patients randomized

2100
Bempedoic acid
180-mg oral dose administered daily

2106
Placebo
Matching placebo

PRIMARY OUTCOME

Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization

FINDINGS

Composite end point occurrence

Bempedoic acid
5.3% (111 of 2100 patients)

Placebo
7.6% (161 of 2106 patients)

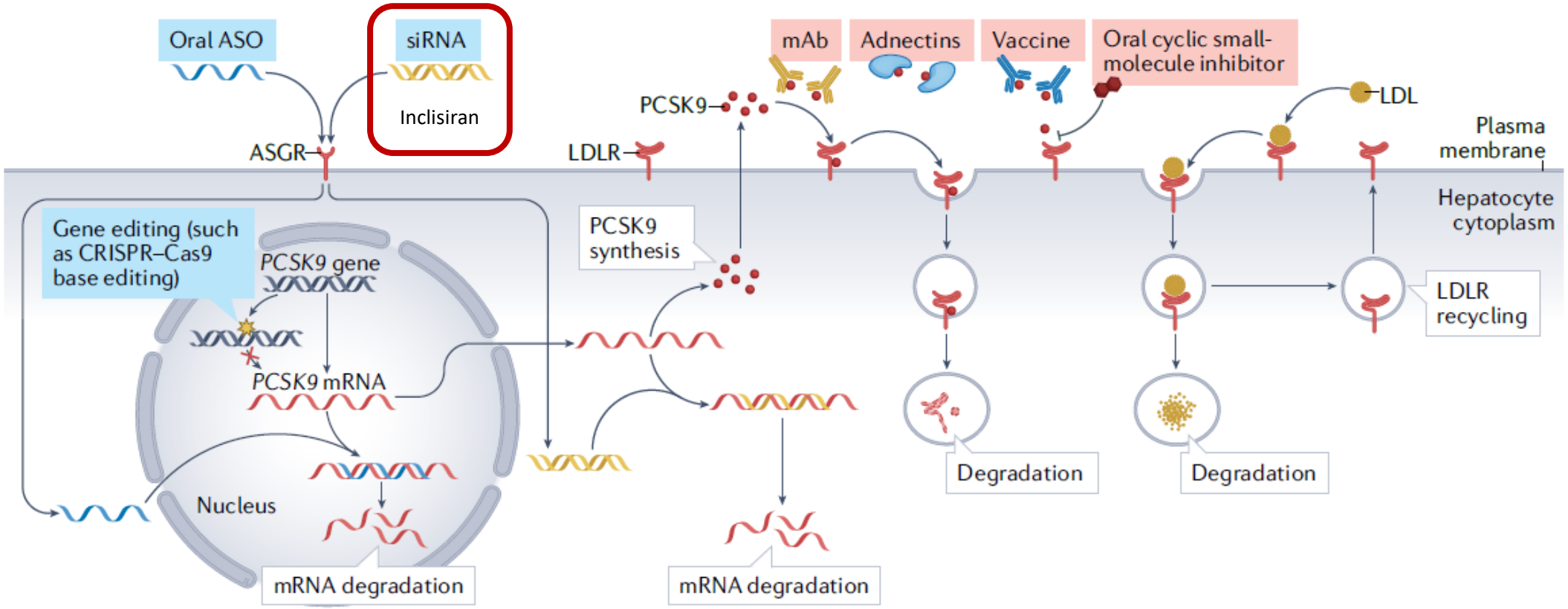
Risk reduction was significant:
Adjusted hazard ratio, 0.70
(95% CI, 0.55-0.89); *P*=.002

JAMA. 2023;330(2):131-140

PCSK9-targeted interventions

12/2021

- Result in degradation of mRNA for PCSK9 in cytoplasm

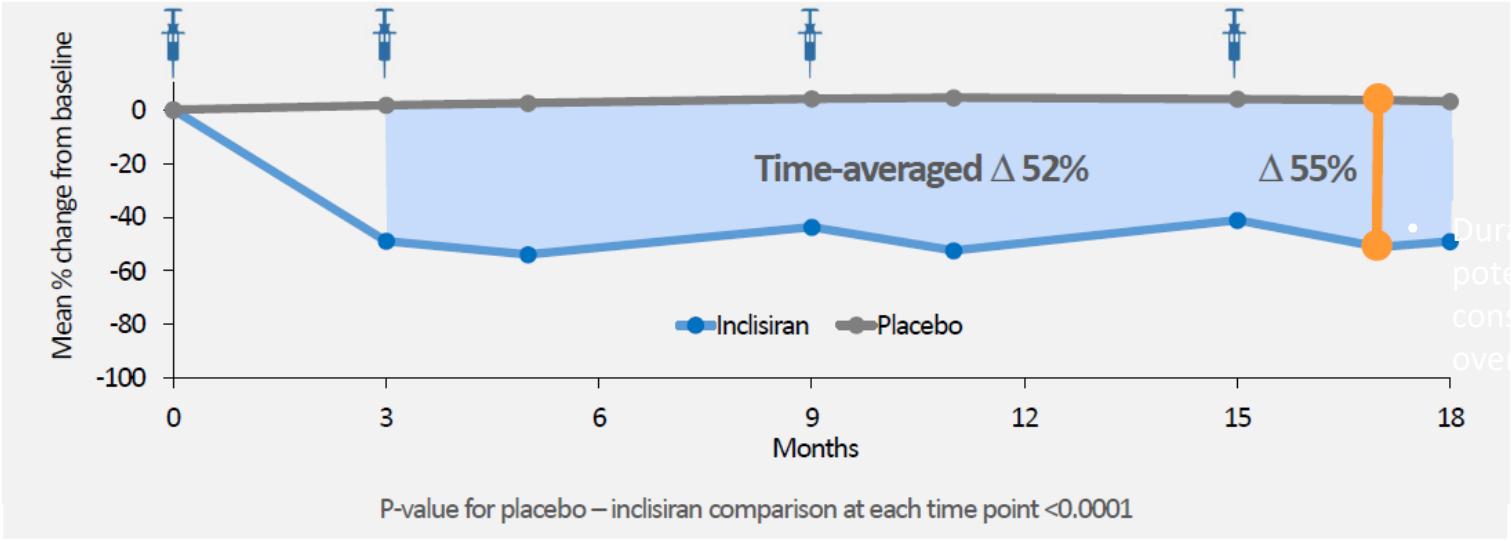


Nature Rev Cardiol.2021;18;805-6

ORION Phase III pooled analysis: Efficacy

ORION-9	ORION-10	ORION-11
HeFH[1]	ASCVD (CHD, CVD, PAD)	ASCVD (CHD, CVD, PAD)
Stable on a low-fat diet		ASCVD risk equivalents • Type 2 diabetes • 10-year risk ≥20% • HeFH[1]

- Percent change in LDL-C over time – observed values in ITT patients



P-value for placebo – inclisiran comparison at each time point <0.0001

J Am Coll Cardiol. 2021;77:1182-93

US FDA approves expanded indication for inclisiran to include treatment of adults with high LDL-C and who are at increased risk of heart disease

July 10, 2023

- *Expanded indication now enables use of inclisiran for LDL-C reduction in patients with primary hyperlipidemia (high LDL-C)*
- *Inclisiran now can be used earlier in LDL-C treatment as an adjunct to diet and statin therapy for patients who have not had a cardiovascular event but are at an increased risk of heart disease*
- *Label update reinforces robust safety and effectiveness data for inclisiran*

East Hanover, N.J, July 10, 2023/PRNewswire/ -- The US Food and Drug Administration (FDA) has approved a label update for inclisiran to enable earlier use in patients with elevated LDL-C who have an increased risk of heart disease, as an adjunct to diet and statin therapy. This patient population includes those who have comorbidities such as hypertension and diabetes and have not yet had a first cardiovascular event

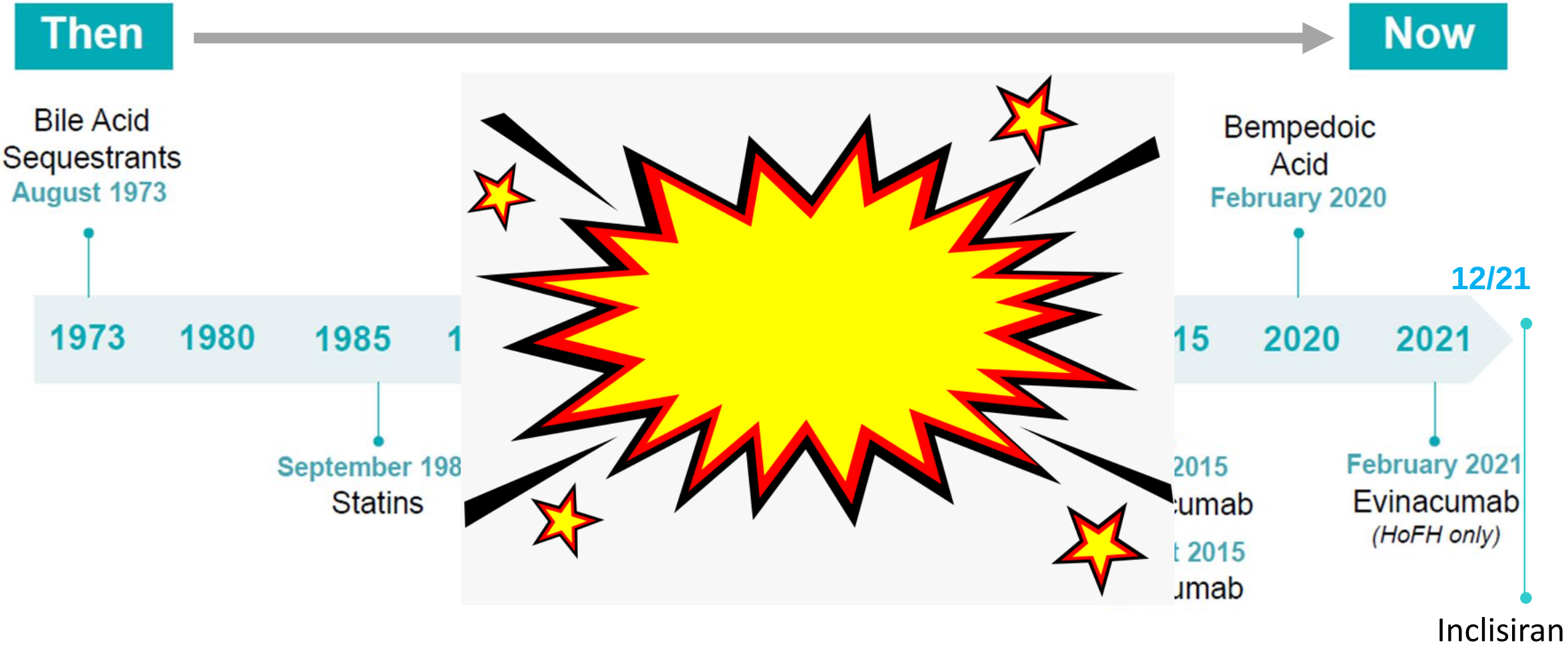
https://www.prnewswire.com/news-releases/us-fda-approves-expanded-indication-for-novartis-leqvio-inclisiran-to-include-treatment-of-adults-with-high-ldl-c-and-who-are-at-increased-risk-of-heart-disease-301872495.html

Ongoing Inclisiran Trials

Trial	Patients	Major Inclusion Criteria	Study Outcomes
ORION-4 (NCT03705234)	N = 15,000	• High-risk ASCVD • ASCVD risk equivalent	CV outcomes trial and long-term efficacy and safety study. Median follow-up of 5 years (2026)
VICTORION-2P	N = 15,000	ASCVD	CV outcomes trial. Up to 72 months (2027)

ClinicalTrial.gov. NCT03705234;
ClinicalTrial.gov. NCT03060577;
ClinicalTrial.gov. NCT03814187;
ClinicalTrial.gov. NCT05030428.

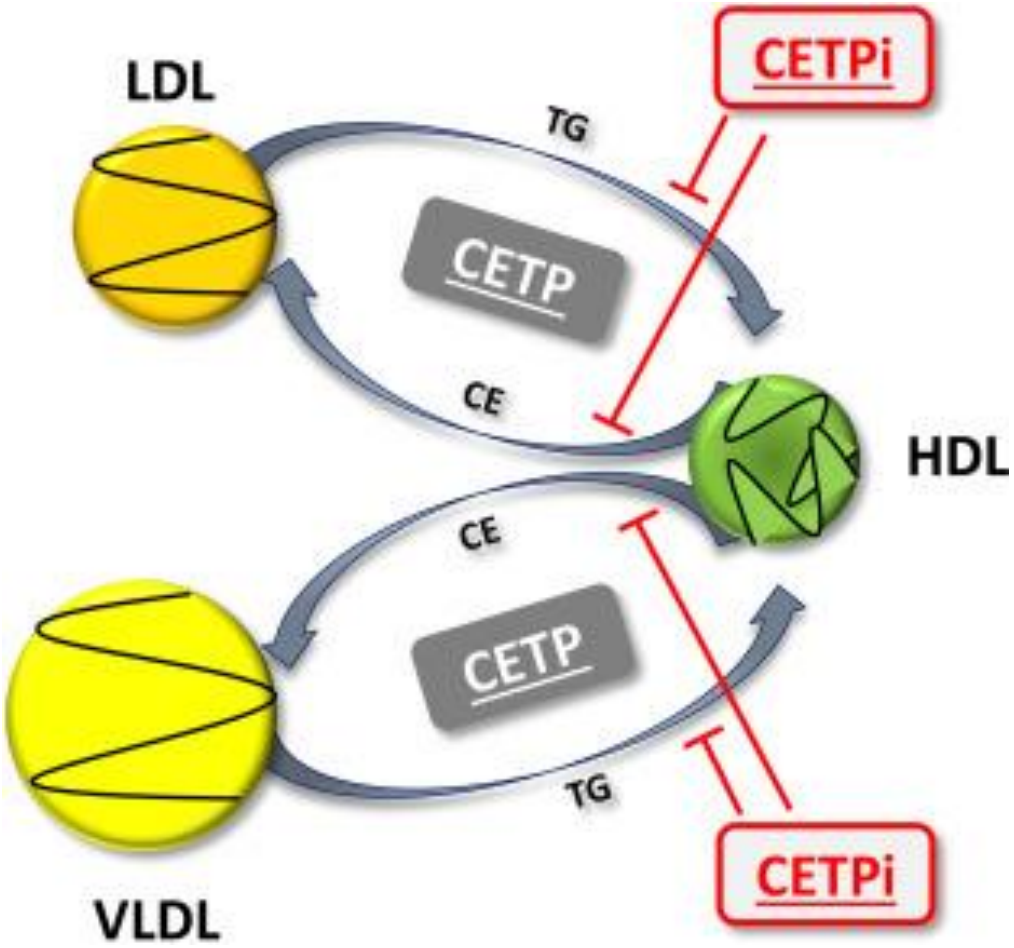
Novel Lipid-Modifying Agents in Development



CETP inhibition

- CETP-inhibiting therapies originally developed based on premise that increasing HDL-C levels would prevent CV events.
  - Promotes transfer CE from HDL to apoB containing lipoproteins

- Data have now suggested that CV benefits related to changes in Apo-B-containing particles (including LDL particles).



CETP inhibition: Obicetrapib

- Obicetrapib is selective CETP inhibitor undergoing clinical development for reducing both LDL-C and incidence of MACE
- At equipotent dosages obicetrapib reduces CETI activity to a greater extent than both anacetrapib and evacetrapib.
  - 5 mg or 10 mg obicetrapib
    - Up to 51% in LDL-C
    - Decreased apoB by up to 30%
    - Decreased non-HDL-C by up to 44%
    - Increased HDL-C by up to 165%
- PREVAIL Trial
  - N=9000
  - Completion: 12/2026

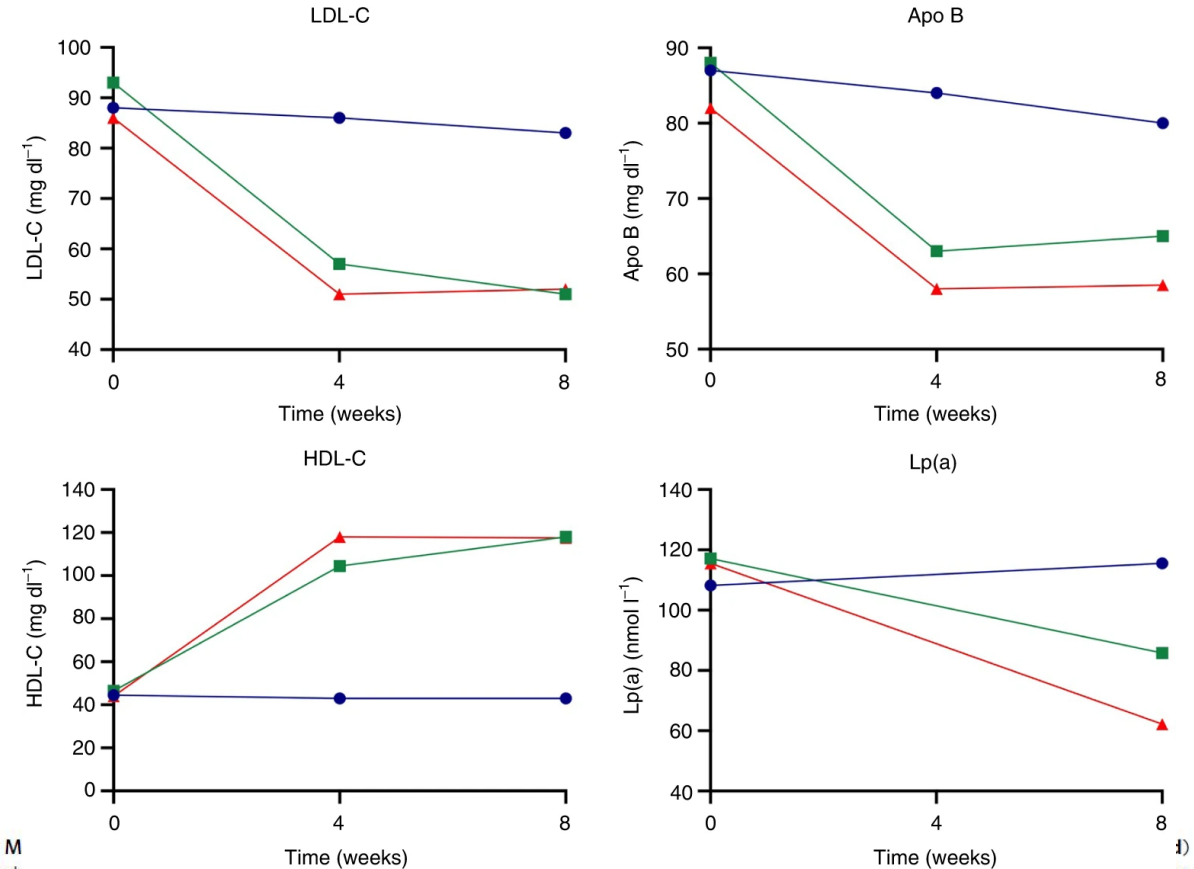
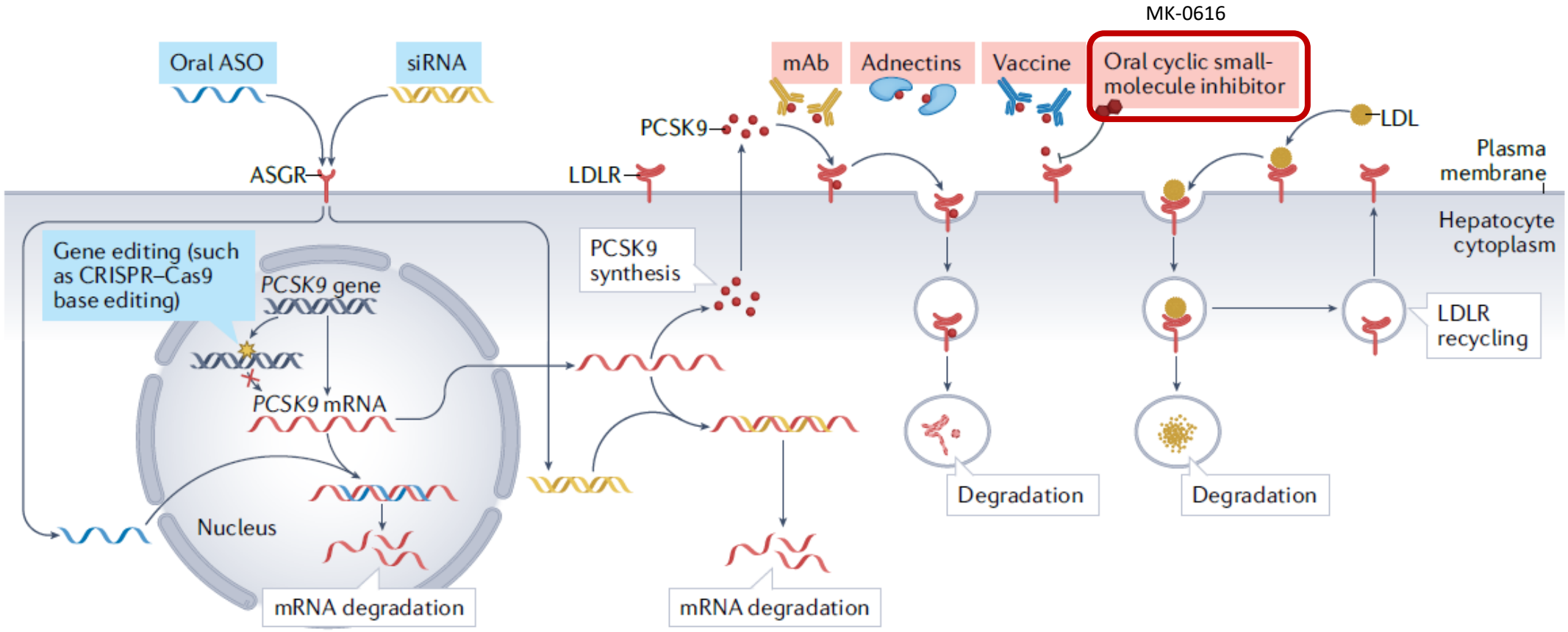


Fig. 2 | M for the placebo (blue), obicetrapib 5 mg (green) and obicetrapib 10 mg (red) groups ($n = 40$ each), administered on a background of high-intensity statin treatment at baseline and after 4 and 8 weeks of treatment (only after 8 weeks of treatment for Lp(a)).

Nature Medicine.2022;28:1672–1678

PCSK9-targeted interventions

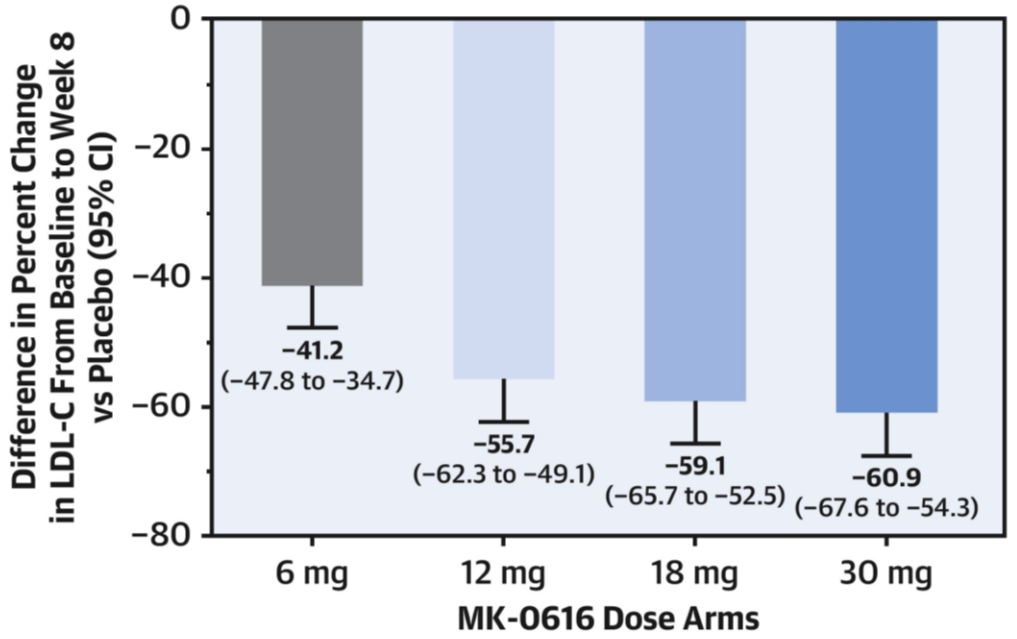


Nature Rev Cardiol.2021;18;805-6

Phase 2b Randomized Trial of the Oral PCSK9 Inhibitor MK-0616

- LDL-C reduction from Baseline to Week 8 superior to placebo ($p<0.001$) for all doses of MK-0616
- Near-complete efficacy achieved by 2 weeks with persistent effect over the 8-week treatment period
- Results generally consistent across prespecified subgroups

Efficacy *(n = 380 Treated Participants)*



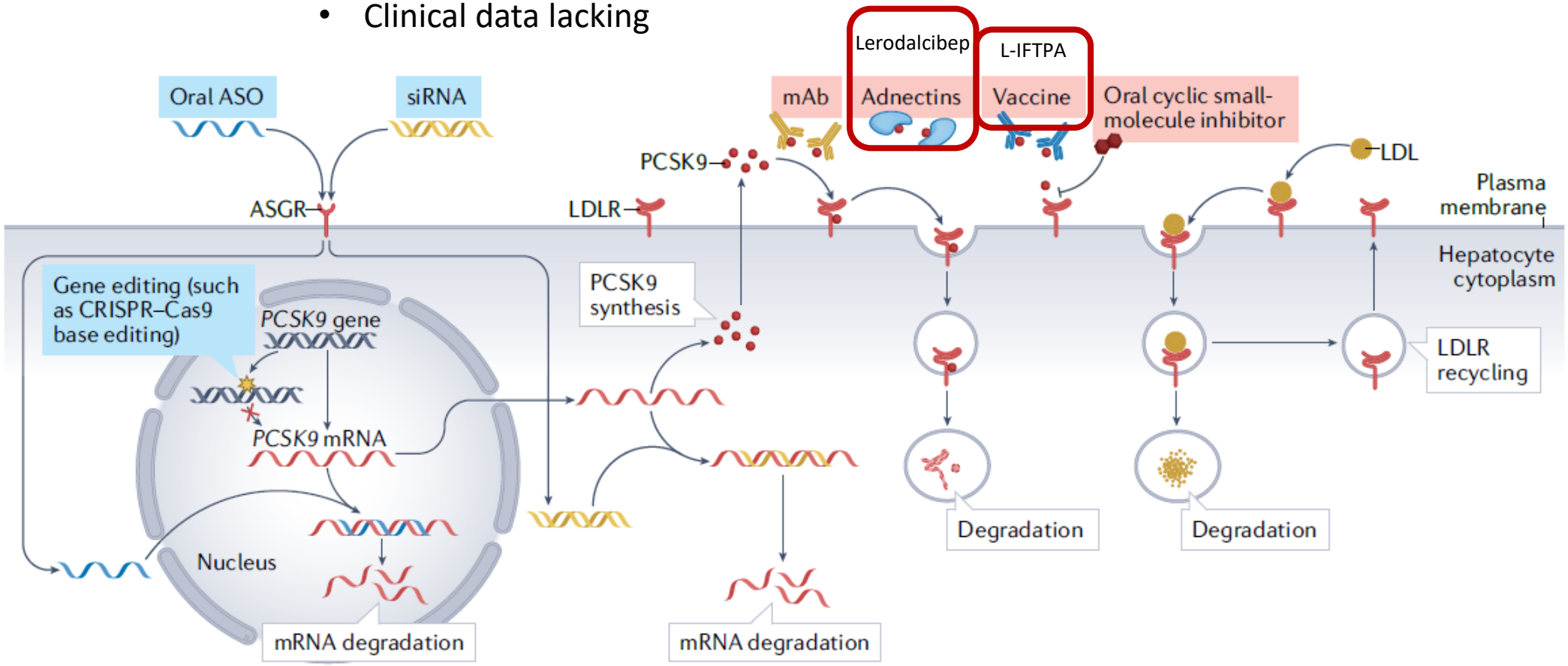
Key Points

- All doses of MK-0616 demonstrated statistically superior reductions in LDL-C vs placebo with up to 60.9% placebo-adjusted reduction from baseline values
- MK-0616 was well tolerated with no overall trends in AEs across treatment groups

J Am Coll Cardiol. 2023 Apr, 81 (16) 1553–1564

PCSK9-targeted interventions

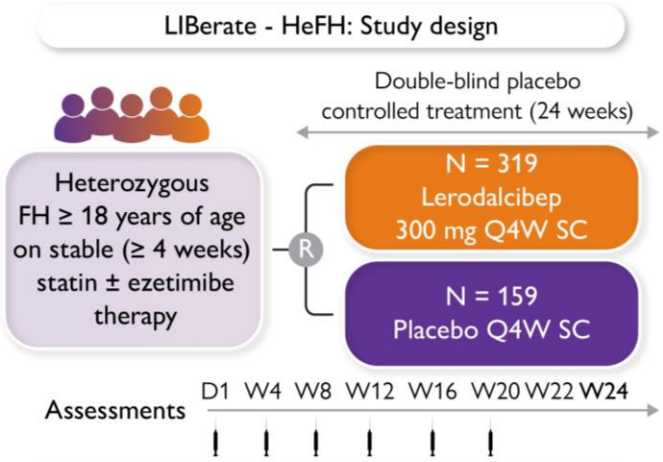
- Vaccines against PCSK9 to trigger generation of host anti-PCSK9 antibodies and neutralize PCSK9/LDLR interactions
- Clinical data lacking

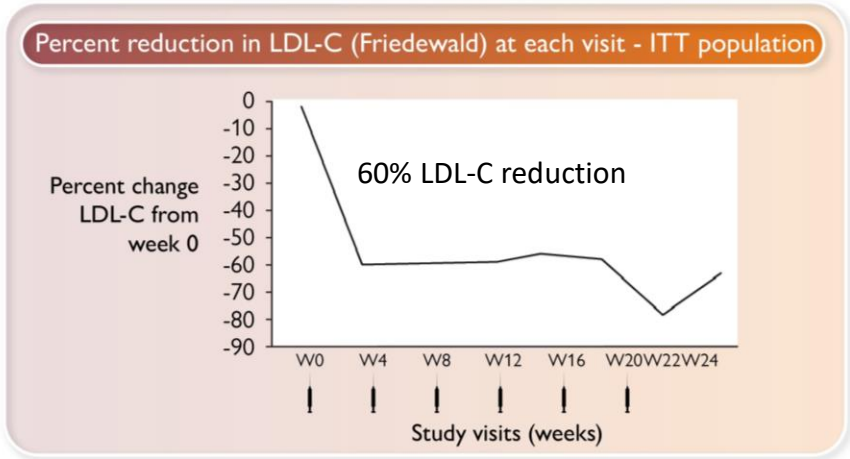


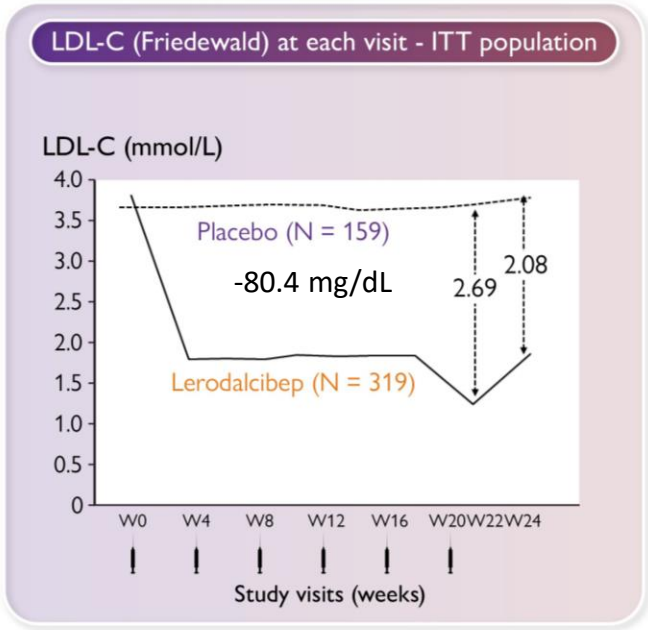
Nature Rev Cardiol.2021;18;805-6

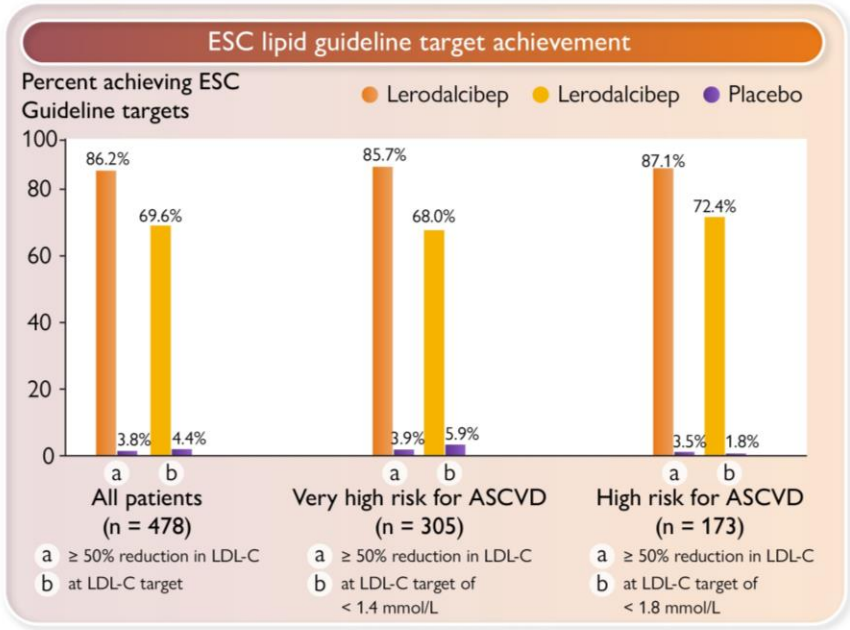
LIBerate-HeFH Study: Lerodalcibep in HeFH

- 300 mg (1.2 ml SC) monthly
- 60% LDL-C reduction
  - 2.08 mmol/L
  - 80.4 mg/dL





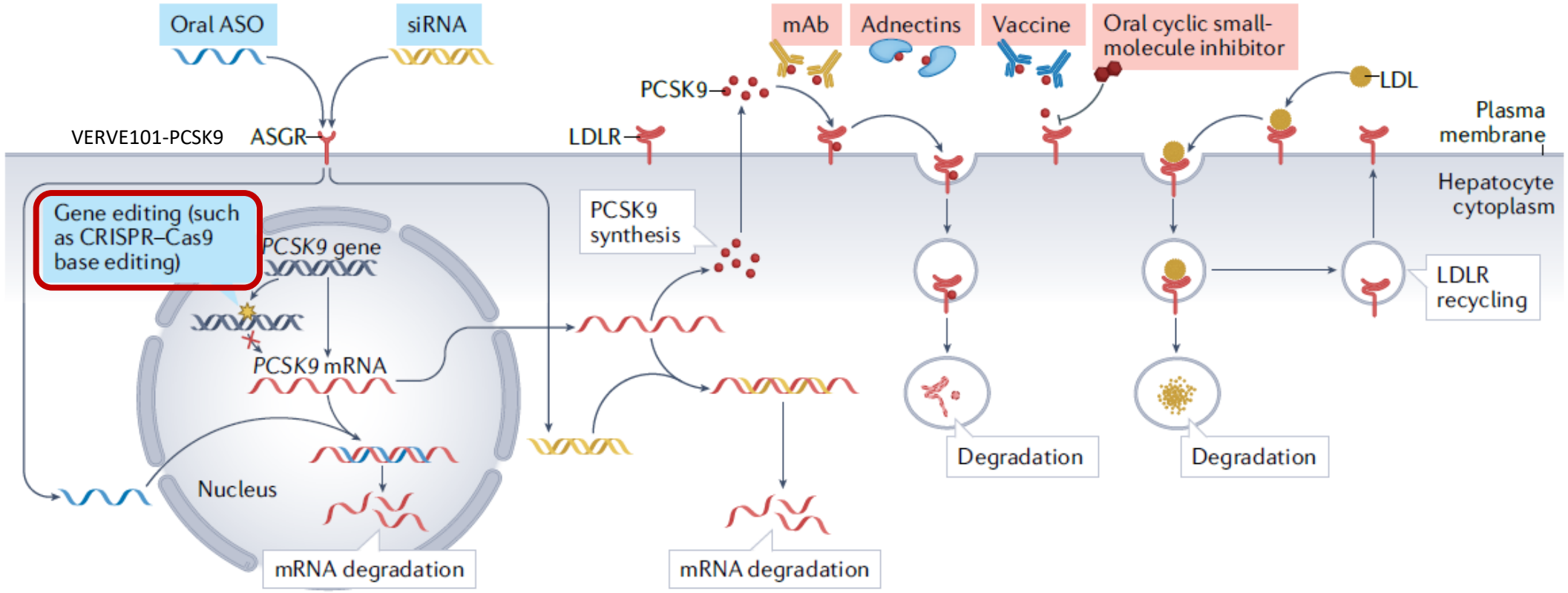




European Heart Journal, ehad596, https://doi.org/10.1093/eurheartj/ehad596

PCSK9-targeted interventions

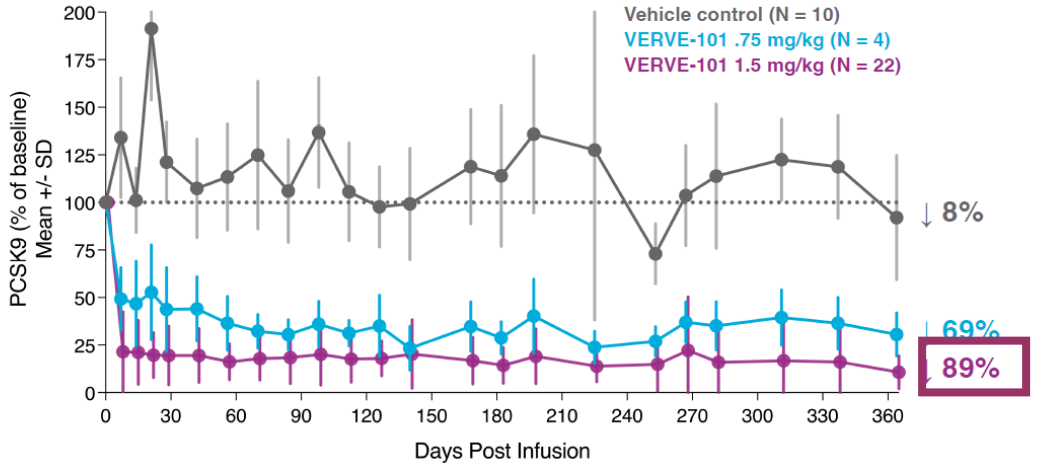
Gene editing technologies: Once and done



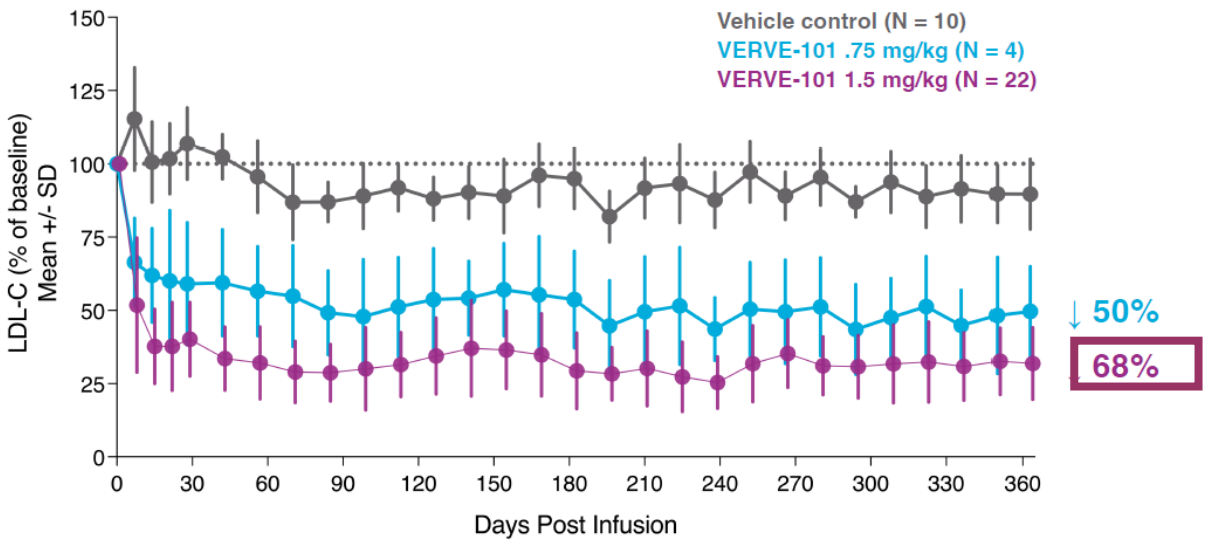
Nature Rev Cardiol.2021;18;805-6

VERVE-101: Non-human primates

VERVE-101 testing in NHPs: 89% reduction blood PCSK9 observed at one year after one-time intravenous infusion



Blood LDL-C level: 68% reduction observed at one year after one-time intravenous infusion of VERVE-101 in NHPs



Courtesy Dr. Sek Kathiresan
Khera A, Circulation 2022

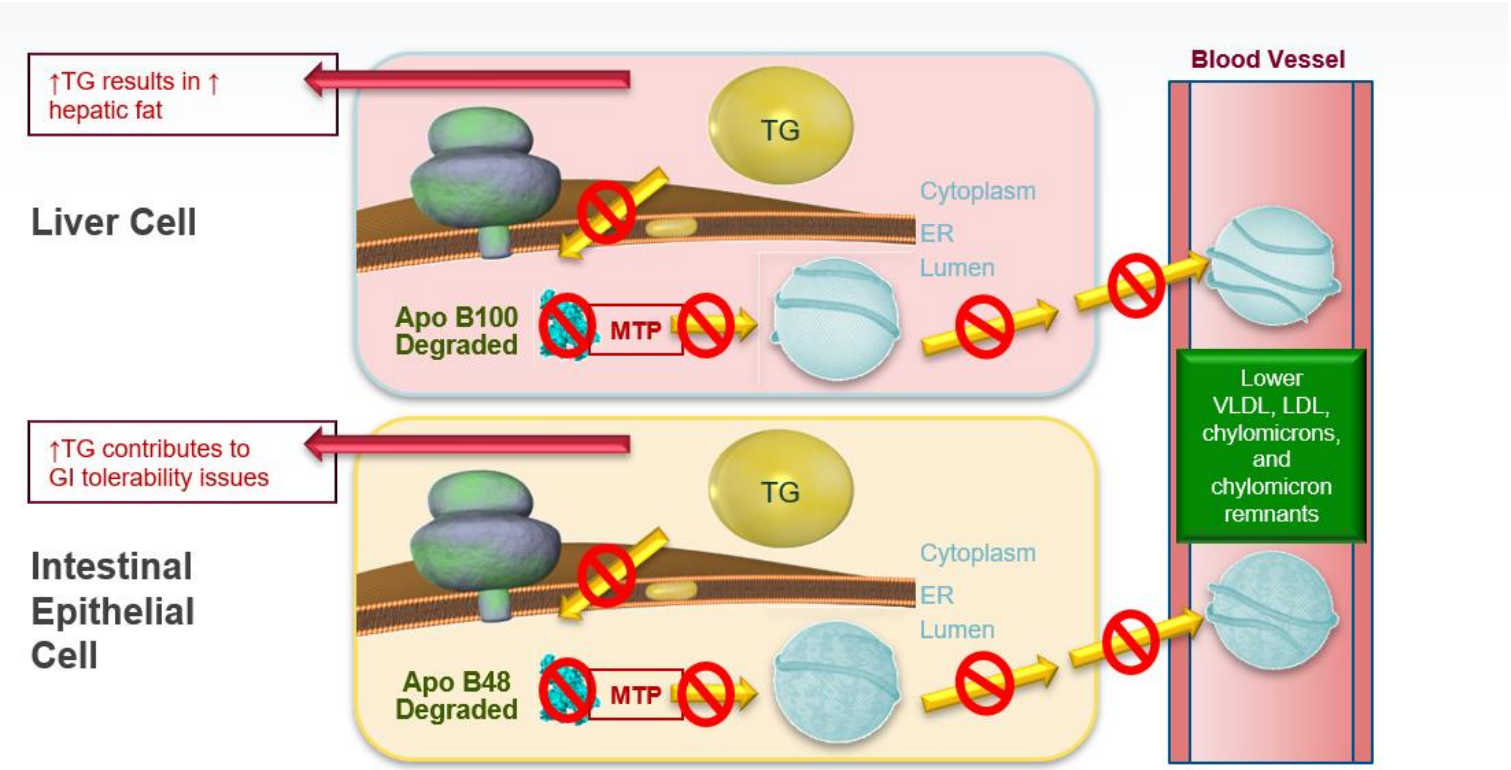
Novel Therapies in HoFH

- Lower LDL-C independently of the LDL receptor

2012

Lomitapide

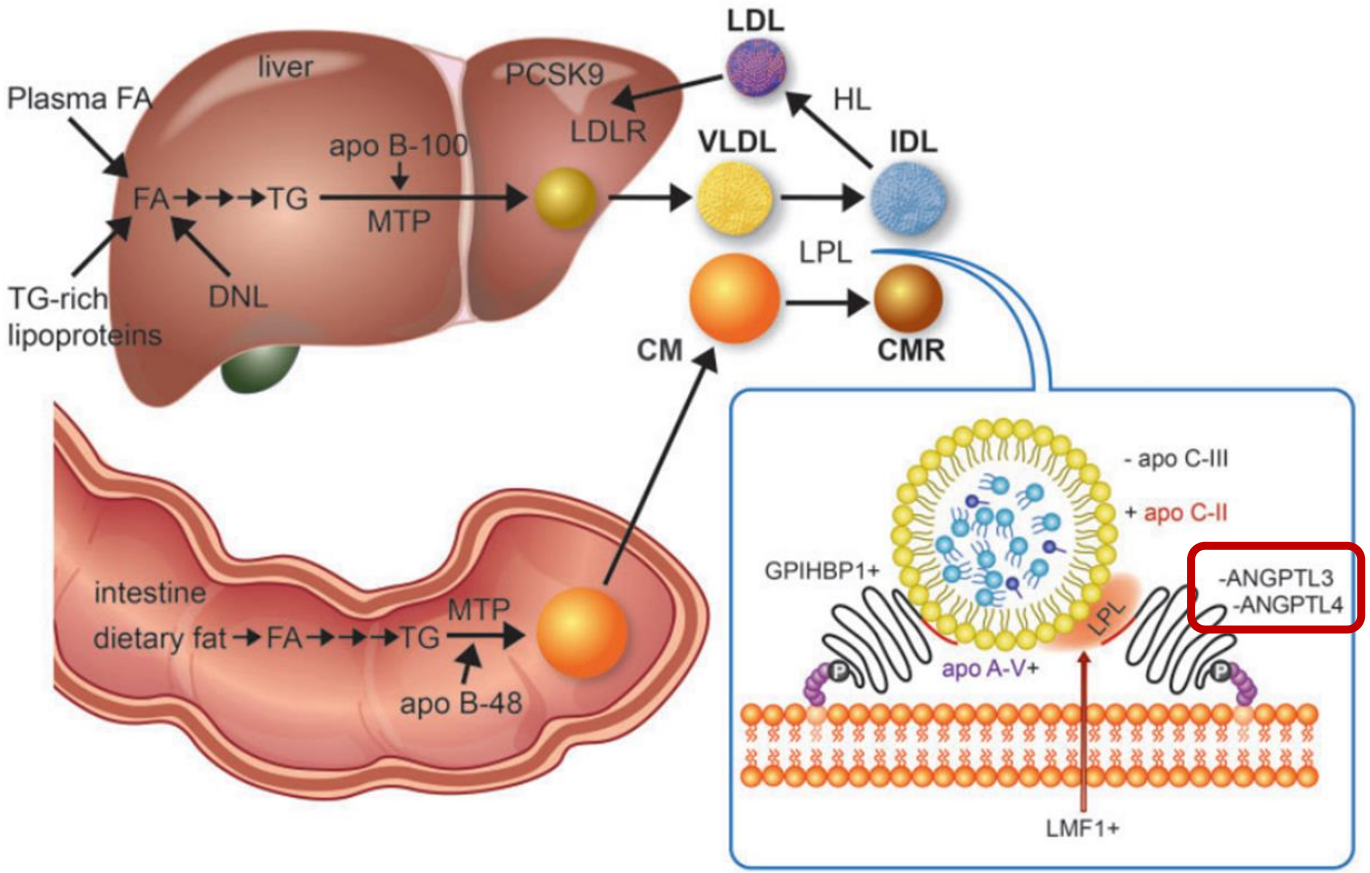
- Inhibitor of MTP
  - Enzyme that lipidates apoB
- FDA-approved in addition to a diet low in fats, and other drugs used to reduce lipids, to decrease LDL-C, apolipoprotein B, and other lipoproteins, in patients with HoFH.
  - Lowers LDL-C 40-50%
- Adverse effects
  - Increase in hepatic fat
  - GI tolerability issues



J Lipid Res. 2003;44:22-32

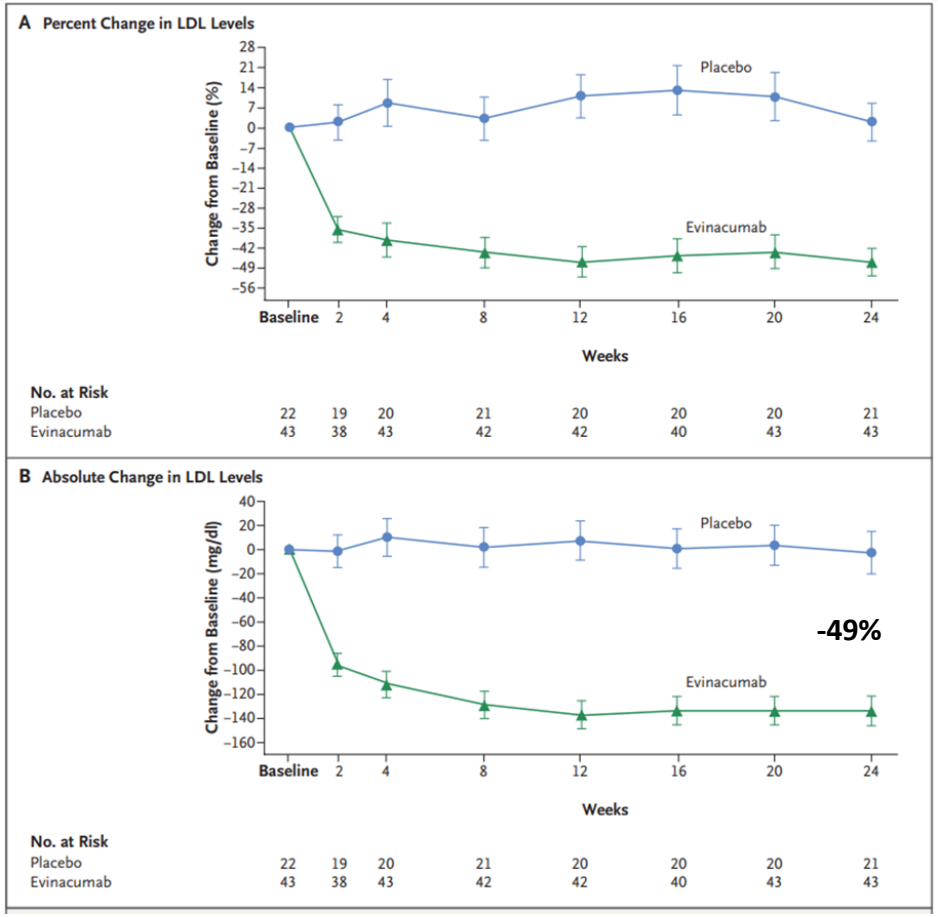
2/2021

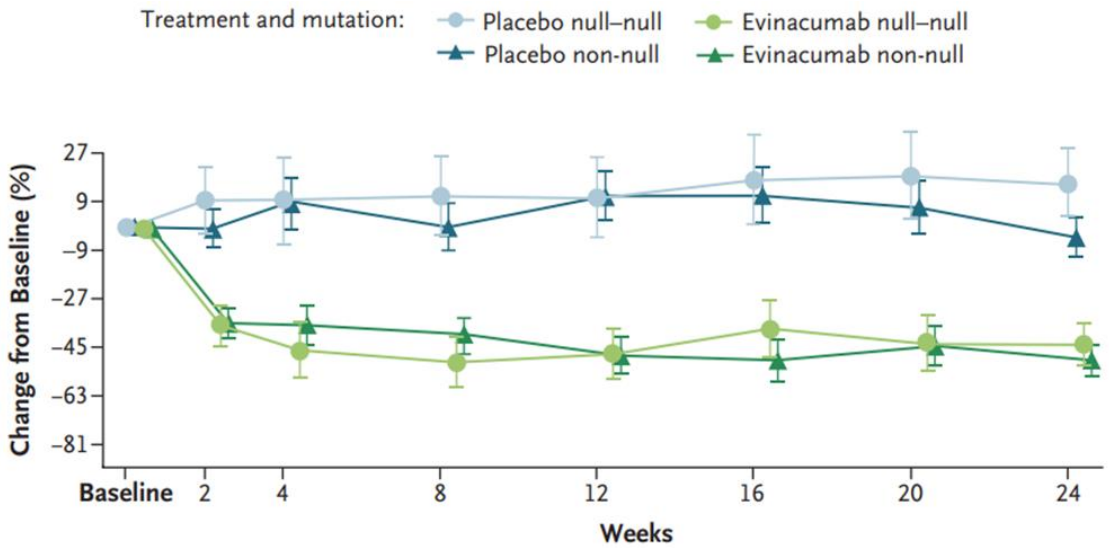
Evinacumab: ANGPTL3 inhibition



- Evinacumab: fully human monoclonal antibody that is an inhibitor of ANGPTL3
- Angiopoietin-like 3 (ANGPTL3) is an inhibitor of LPL and EL
  - Plays a key role in lipid metabolism by increasing the levels of TGs and other lipids
- Loss-of-function variants associated with low levels of both LDL-C and TGs
  - 41% lower risk of CAD, despite presence of low levels of HDL-C
- Both ANGPLT3 loss-of-function variants and ANGPTL3 pharmacologic inhibition reduce LDL-C levels *independently of the LDL receptor*.

Evinacumab in HoFH





No. at Risk								
Placebo null–null	6	4	6	6	6	6	6	6
Placebo non-null	16	15	14	15	14	14	14	15
Evinacumab null–null	15	14	15	15	14	15	15	15
Evinacumab non-null	28	24	28	27	28	25	28	28

N Engl J Med 2020;383:711-20.

Summary:

- Foundation of therapy remains statins
- Evidence-based non-statins
  - Ezetimibe
  - PCSK9mAB
  - Bempedoic acid
- FDA approved therapy with CVOTs in progress
  - Inclisiran

- Therapies approved in HoFH only
  - Lomitapide
  - Evinacumab
- Novel therapies in development
  - Obicetrapib
  - MK-0616
  - ASO/siRNA therapies [PCSK9, ANGPTL3]
  - Gene editing

Thank you!

Case Presentation

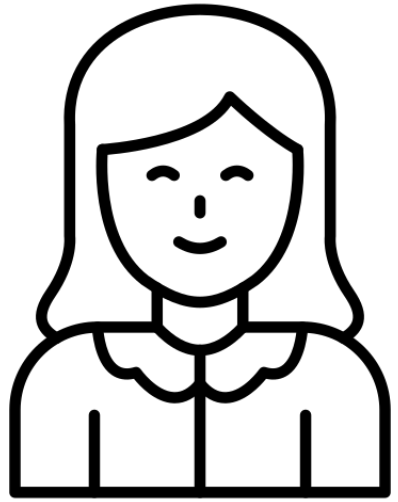
Pamela B. Morris, MD, FACC, FAHA, FASPC, FNLA
Professor of Medicine, Cardiology
Paul V. Kramer Chair of Cardiovascular Disease Prevention
Director, Seinsheimer Cardiovascular Health Program
The Medical University of South Carolina

@PamelaBMorris

Disclosures

- Local PI (Esperion, CLEAR Outcomes)

Case Presentation



- 34 yo woman returns for f/u
- Has known severe HeFH (LDL receptor variant)
- Family History
  - Paternal Grandmother: HeFH, first MI in 30's, CABG age 40 yrs, died of stroke at 53 yrs
  - Father: HeFH, CABG age 52 yrs
  - Paternal uncles: HeFH, ASCVD
  - Brother: died of MI age 30 yrs
- Diagnosed with HeFH in adolescence, treated with statin since late teenage yrs other than during conception, pregnancy, lactation

Case Presentation

- Initially presented at age 28 yrs to reinitiate therapy
- First child was 1 year old, breastfeeding completed

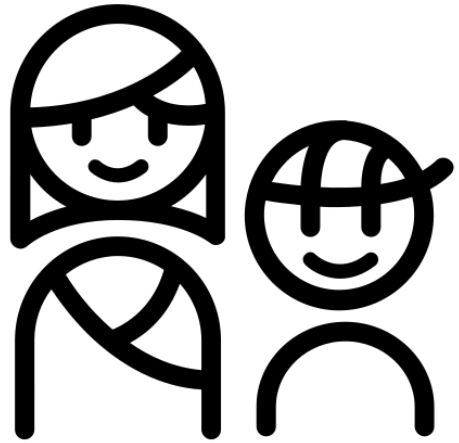
- Labs
  - TC 389 mg/dL
  - TG 95 mg/dL
  - HDL-C 58 mg/dL
  - LDL-C 312 mg/dL
  - Lp(a) 124 nmol/L

Case Presentation

- Therapy initiated
  - Rosuvastatin 40 mg, ezetimibe, evolocumab

- Repeat labs
  - TC 168 mg/dL
  - TG 85 mg/dL
  - HDL-C 54 mg/dL
  - LDL-C 97 mg/dL

Case Presentation



- 2 years later patient returns (age 30 yrs)
- Desires 2nd pregnancy
- Medications discontinued
  - Previously unable to tolerate colesevelam

Case Presentation

- 2 years later patient returns (age 30 yrs)
- Desires 2nd pregnancy
- Medications discontinued
  - Previously unable to tolerate colesevelam
- Uncomplicated 2nd pregnancy
- Medications reinitiated

Case Presentation

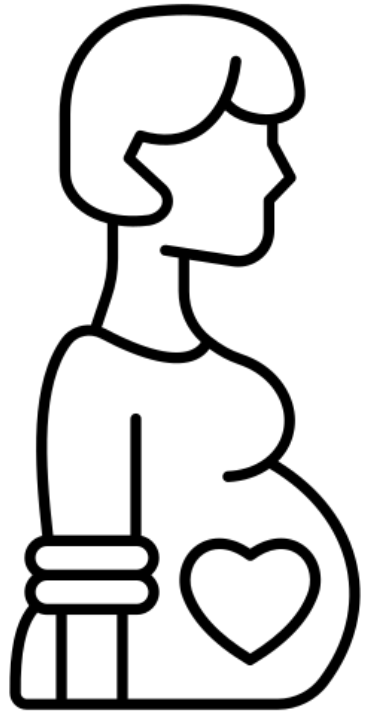
- Age 32 yrs, desires final pregnancy
- Age 34 yrs, uncomplicated 3rd pregnancy
  - Returns for reinitiation of therapy

Case Presentation

- Shortly after reinitiation of therapy…
- Patient presents with chest pain to ED
  - ECG: NSSTTWC
  - Mild elevation of troponin
  - LHC: culprit lesion in LAD, 90% RCA, >moderate LCx (FFR+)
  - Underwent CABG x 3

Case Presentation

- Questions for consideration
  - What are best practices for management of women with FH in childbearing years?
  - What is the association between Lp(a) and FH?
  - What is role of preventive imaging in young adults with FH?



Thank you!

Exploring Novel Strategies for LDL-C Combination Therapy to Decrease ASCVD Risk: A Paradigm Shift

Case #2

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Disclosures

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  - Impact of time-restricted feeding (TRF) on glucose homeostasis and mitochondrial function in patients with metabolic syndrome – The TIMET Study (NCT0405733)
- Hillblom Network Grant (PI: Taub PR) (NCT05365529)
- Dysautonomia International Grant (PI: Taub PR) (NCT05409651)

Clinical Trial Leadership:

- US National Lead/Steering Committee Member for: Study of Inclisiran to Prevent Cardiovascular (CV) Events in Participants With Established Cardiovascular Disease (VICTORION-2P). (Sponsor: Novartis; NCT05030428)
- US National Lead/Steering Committee Member for: A Double-blind, Randomized, Placebo controlled, Multicenter Study Assessing the Impact of Olpasiran on Major Cardiovascular Events in Patients with Atherosclerotic Cardiovascular Disease and Elevated Lipoprotein (a). (Sponsor: Amgen NCT05581303)
- Global Executive Steering Committee Member for VICTORIAN-1P Trial (Sponsor: Novartis)
- National Principal Investigator for the NIH RECOVER COVID Initiative (recovercovid.org) and responsible for design and execution of studies related to Post COVID Postural Orthostatic Tachycardia Syndrome.
- US National Lead/Steering Committee Member for MK0616 (oral PCSK9 inhibitor) Phase 3 program (Sponsor: Merck)
- Executive Steering Committee Member for TRANSFORM Trial (Sponsor: Cleerly)

Case Presentation

- 62 year old female with HTN, T2DM, atrial fibrillation, and hypothyroidism.
- Her past medical history is notable for preeclampsia with both of her pregnancies.

- Current medications: atorvastatin 40 mg, amlodipine 10 mg, levothyroxine 75 mcg, apixaban 5 mg bid, metformin 500 mg bid, empagliflozin 10 mg qd
- Exam: Blood Pressure: 110/85 HR 70; BMI 30 kg/m^2
- Laboratory Data:

Total Cholesterol: 140 mg/dL

HDL: 30 mg/dL

Calculated LDL: 53 mg/dL

Triglycerides: 287 mg/dL

Non-HDL: 110 mg/dL

HbA1c: 7.0

Creatinine 1.4 mg/dL;

eGFR 55 mL/min

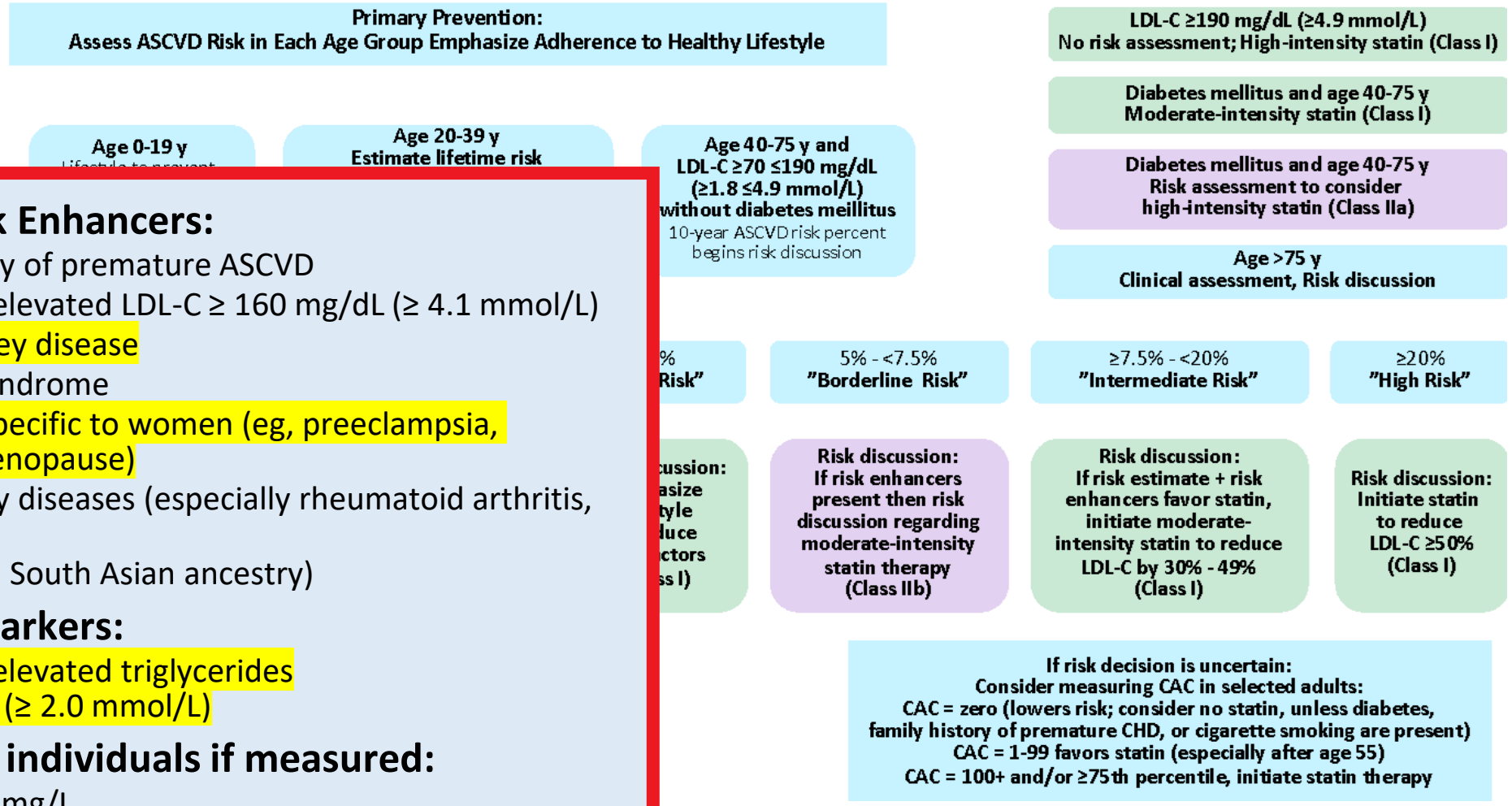
ARS Question

What do you recommend?

A. **Reassure her and tell her that the LDL is in range**
B. **Increase atorvastatin to 80 mg**
C. **Add fenofibrate**
D. **Increase metformin to 1000 mg bid**
E. **Inrease empaglifozin to 25 mg**

2018 Blood Cholesterol Guideline

ASCVD Risk Enhancers



ASCVD Risk Enhancers:

- Family history of premature ASCVD
- Persistently elevated LDL-C ≥ 160 mg/dL (≥ 4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (eg, preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (eg, South Asian ancestry)

Lipid/Biomarkers:

- Persistently elevated triglycerides (≥ 175 mg/dL, (≥ 2.0 mmol/L)

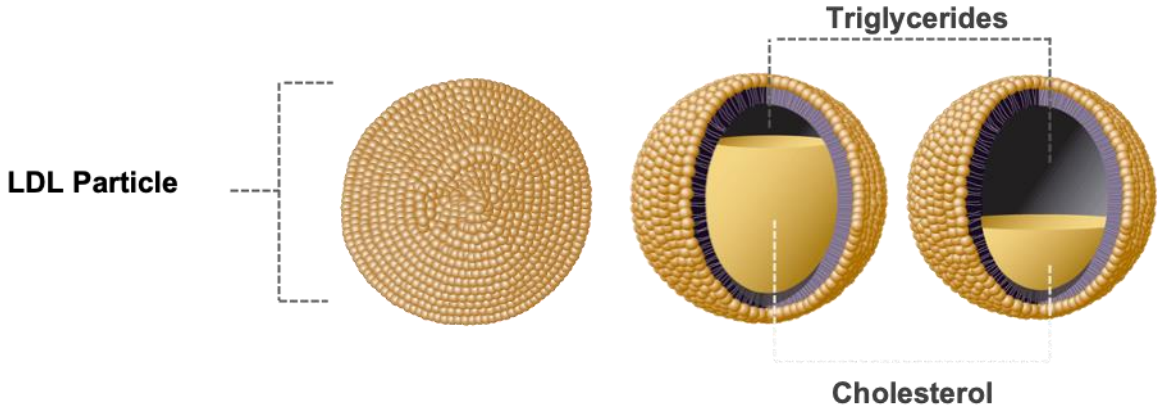
In selected individuals if measured:

- hs-CRP ≥ 2.0 mg/L
- Lp(a) levels > 50 mg/dL or > 125 mmol/L
- apoB ≥ 130 mg/dL
- Ankle-branchial index (ABI) < 0.9

Grundy SM, et al. *J Am Coll Cardiol.* 2018; S0735-1097(18)39034-X

Beyond LDL Cholesterol

- LDL-C: amount of cholesterol in LDL particles
- LDL-P: number of LDL particles
- Apo-B: reflection of number of atherogenic particles
- Non-HDL: (Total cholesterol - HDL) amount of cholesterol in atherogenic particles
- Low HDL and high TG are associated with higher LDL-P
  - If triglycerides are high there will be less space for cholesterol and it may take more LDL particles to carry a given amount of cholesterol



Management of this patient

- This patient is prescribed atorvastatin 80 mg daily and also started on icosapent ethyl 2 g bid
- Lifestyle management including: aerobic exercise, Mediterranean diet avoidance of concentrated sugars/alcohol is discussed with the patient.

3 Months later

- She states her younger brother who is 44 has had stroke.
- She then gets a coronary calcium score done that shows an elevated coronary calcium score of 1200

ARS Question

What do you recommend for this patient based on this recent data?

A. Reassure her and tell her no further testing is needed and to continue atorvastatin 80 mg.

B. Check myeloperoxidase

C. Check Lipoprotein-associated phospholipase A_2 (Lp-PLA_2)

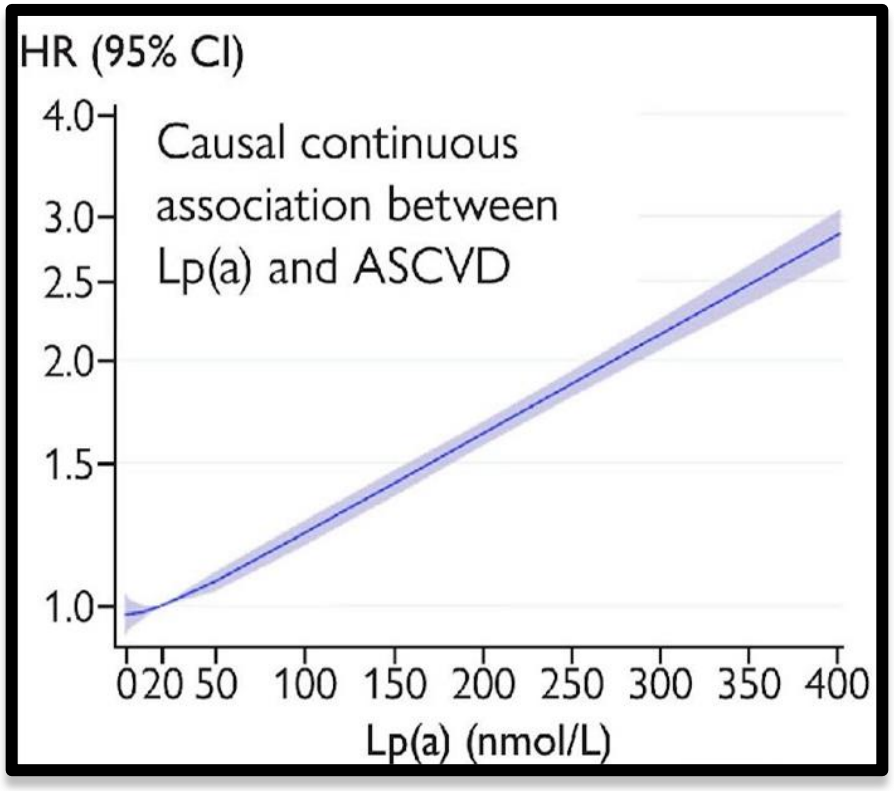
D. Check lipoprotein A

Use of Lp(a) in Clinical Practice

Elevated Lp(a) > 50 mg/dL or > 125 nmol/L

National Lipid Association

- Primary prevention - adults & youth with:
  - First-degree relatives with premature ASCVD or elevated Lp(a)
  - History of premature ASCVD and/or ischemic stroke
  - **Primary severe hypercholesterolemia** or **suspected familial hypercholesterolemia**
- Secondary prevention – adults with:
  - **Premature ASCVD**
  - Recurrent or progressive ASCVD despite optimal lipid-lowering
  - Calcific valvular aortic stenosis
  - Less-than-expected LDL-C response to statins



European Atherosclerosis Society

"Lp(a) should be measured at least once in all adults."

NLA, National Lipid Association; EA, European Atherosclerosis Society

Wilson DP, et al. *J Clin Lipid,* 2019. 13(3):374–392; Kronenberg F. et al. *Eur Heart J.* 2022; 43(39): 3925–3946.

ARS Question

Based on the elevated coronary calcium score what is your LDL goal for this patient?

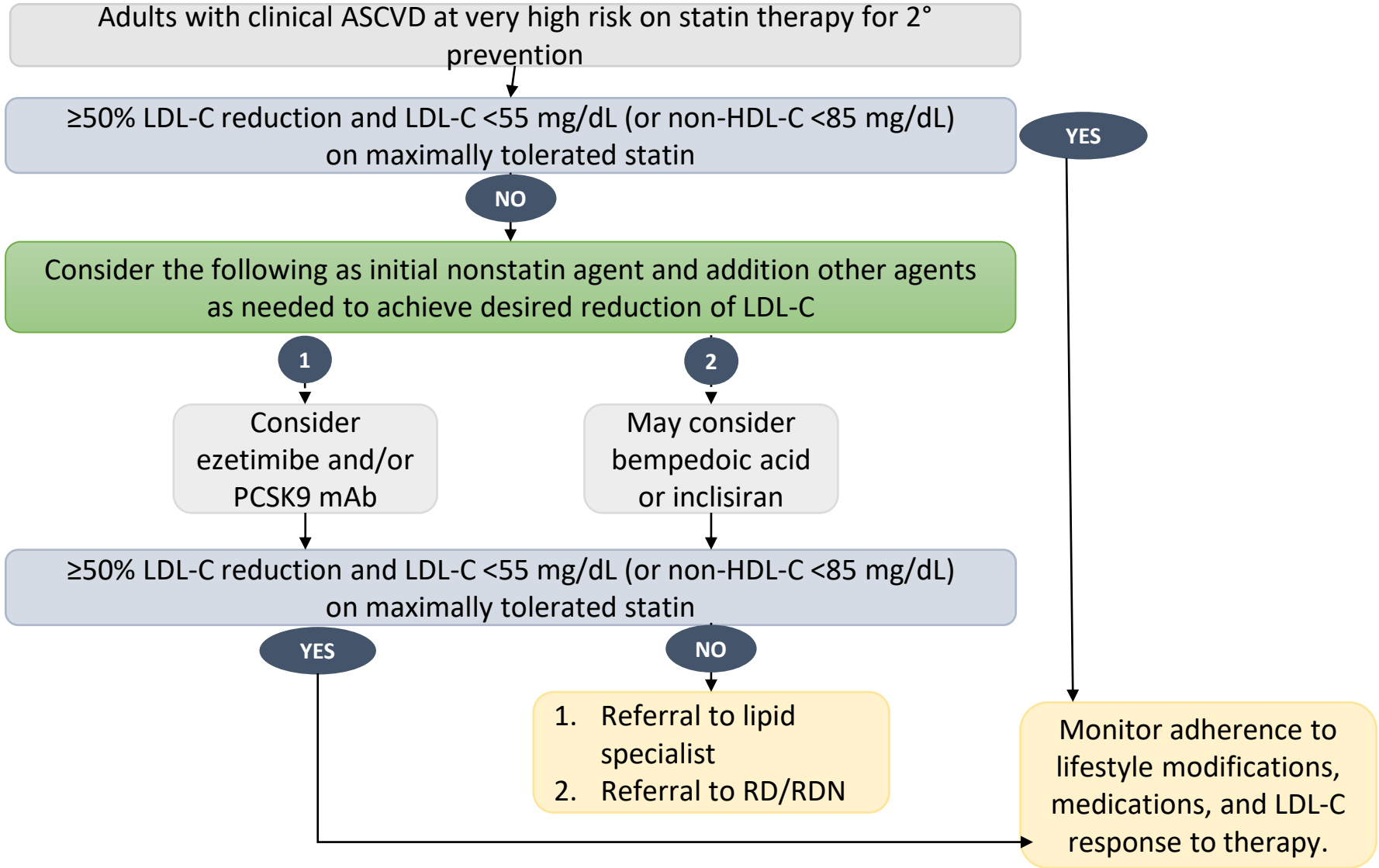
A. LDL <130 mg/dl

B. LDL <100 mg/dl

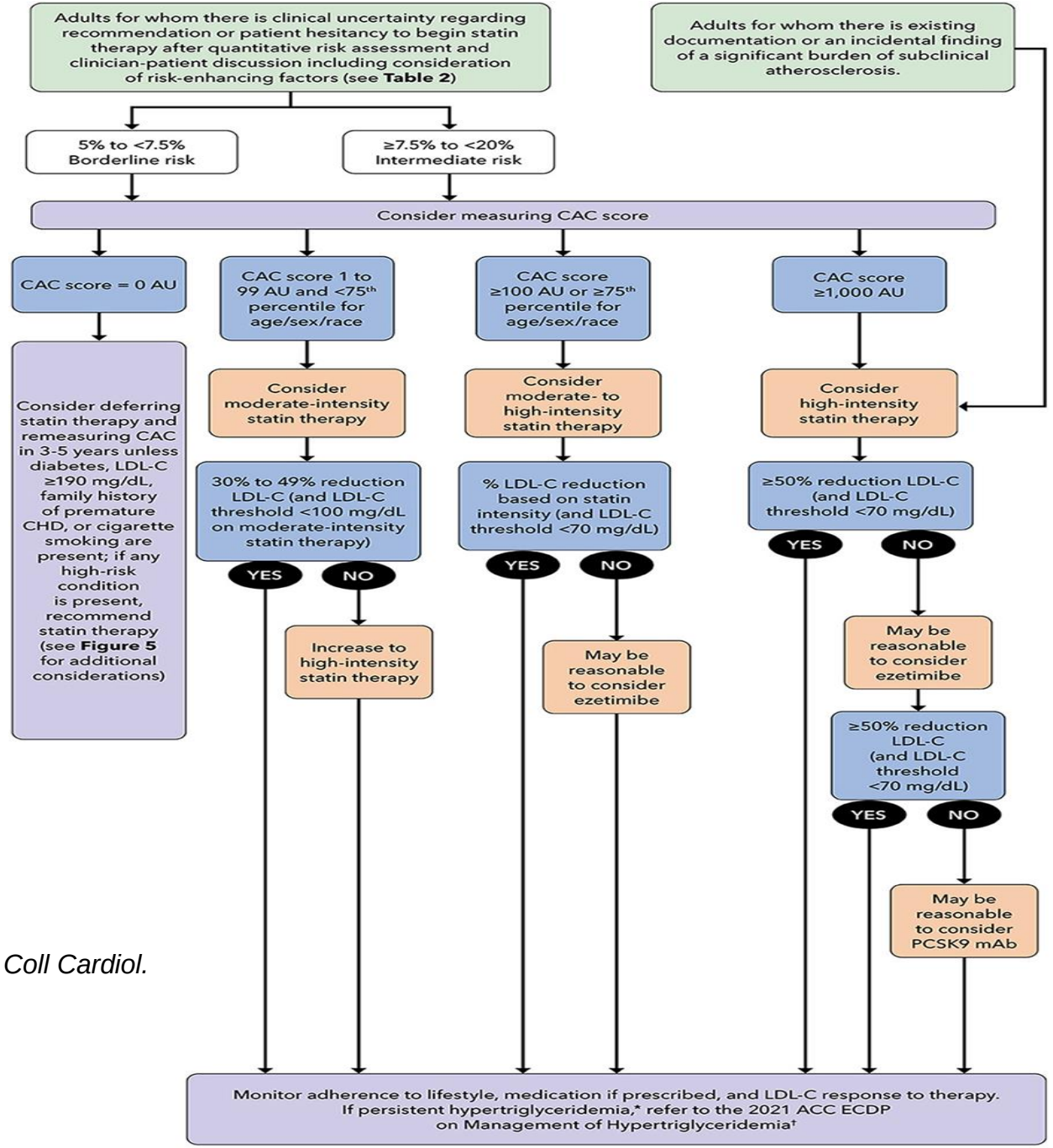
C. LDL <90 mg/dl

D. LDL <70 mg/dl

2022 ACC Expert Consensus Decision Pathway



Lloyd-Jones DM, Morris PB, et al. *J Am Coll Cardiol.* 2022;S0735-1097(22)05594-2.



Lloyd-Jones DM, Morris PB, et al. *J Am Coll Cardiol.* 2022;S0735-1097(22)05594-2.

Case 3

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- **Consultant:** Abbott Diagnostics, Alnylam Pharmaceuticals, Althera, Amarin, Amgen, Arrowhead, Astra Zeneca, Denka Seiken, Esperion, Genentech, Gilead, Illumina, Ionis, Matinas BioPharma Inc, Merck, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche Diagnostic, TenSixteen Bio

Case 3

- 54-year-old South Asian male with family history of diabetes and heart disease is seen in follow up after PCI last month to RCA, had PCI to LAD 2 years ago
- Past Medical History; HTN, mixed hyperlipidemia both treated aggressively after first PCI, impaired fasting glucose.
- Social History: Patient is an executive in a high-pressure job, travels extensively for work, 3 children with many activities and says that his schedule makes if very difficult to get regular exercise. Diet when travelling is not optimal.
- **PE:** Height 5'10", weight 185 lb, BMI 26.5 kg/m^2, waist 36”, BP 125/80 mm Hg
- **Medications:** rosuvastatin 40 mg/d, ezetimibe 10 mg/d, valsartan 160 mg/d, amlodipine 5 mg/d, ASA 81 mg/d, ticagrelor 90 mg b.i.d.
- **Lipids:** LDL-C 65 mg/dL, TGs 140 mg/dL, HDL-C 30 mg/dL, non-HDL-C 94 mg/dL
- **Other labs:** FBG 110 mg/dL, HbA1C 6.1%, eGFR 95

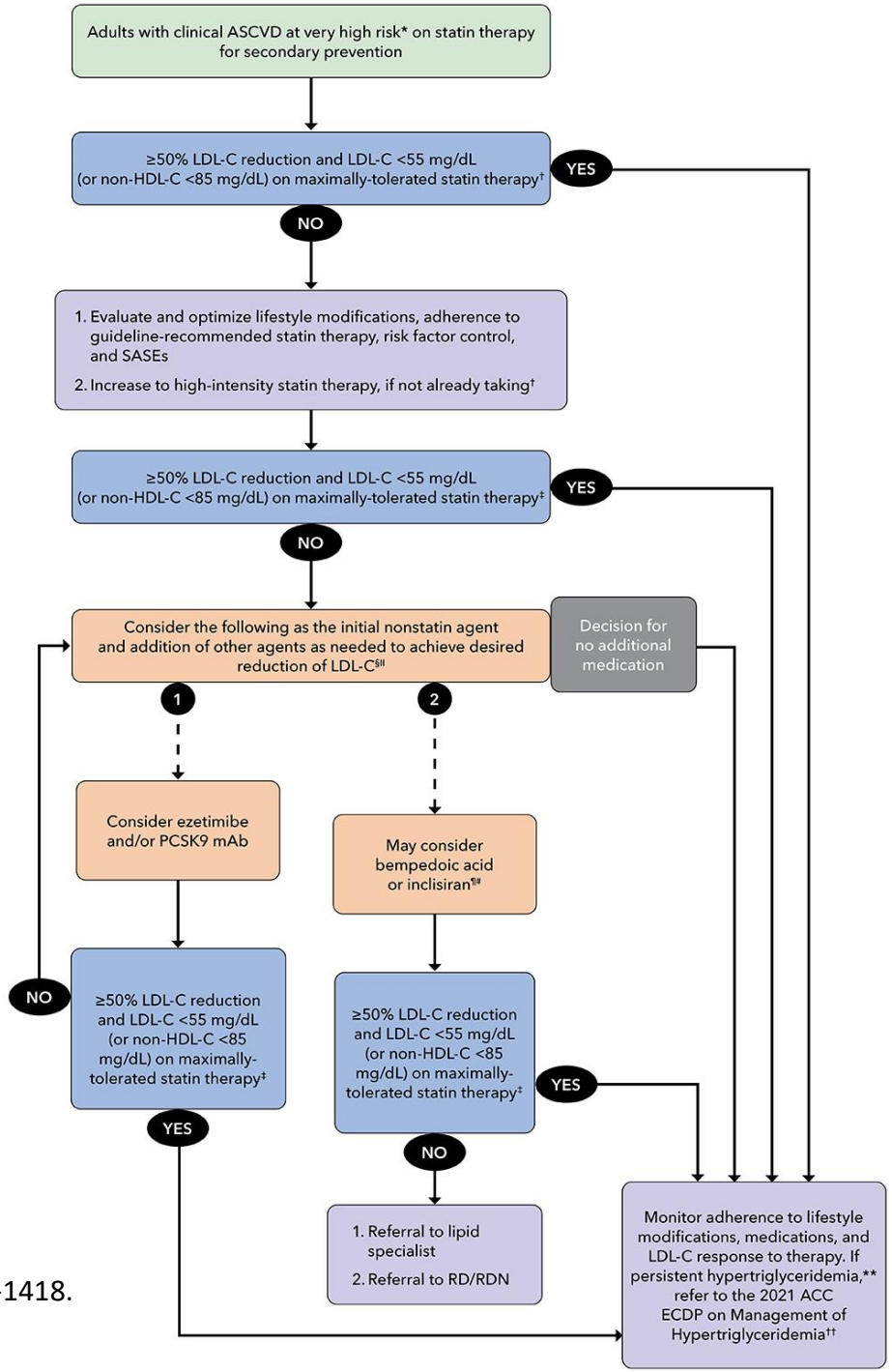
- What are your recommendations re lifestyle changes for this patient?
- What is the LDL-C/Non HDL-C goal for this patient?
- What degree of LDL-C reduction is required to get this patient to goal?
- What other labs would you measure?

Very-High-Risk ASCVD Patients

Major ASCVD Events
Recent ACS (within the past 12 mo)
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)
High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

Grundy SM et al. *J Am Coll Cardiol* 2019;73:e285–e350.

2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-C Lowering in the Management of ASCVD Risk:
Adults with Clinical ASCVD at Very High Risk on Statin for Secondary Prevention



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

Additional laboratory results

hsCRP – 3.2 mg/dl

Apo B – 85 mg/dL

Lp(a) – 185 nmol/L

Reference Here

How would you adjust LLT for this patient?

- What is important to the patient? What has been the patient's experience with past/current LLT?
- Medication adherence in the long-term – common challenges and ways to overcome
  - *Patient: complains of taking too many pills and sometimes forgets; does not want to give himself injections, travels a lot for work*

How would you adjust LLT for this patient?

A. PCSK9 monoclonal antibody inhibitor

B. Inclisiran

C. Bempedoic Acid

Choice of LLT for this patient and why?

- PCSK9 inhibitor discussion? Choice of monoclonal antibody?
- Role of inclisiran?
  - Concerns re MOA; efficacy/safety in ASCVD
- Bempedoic acid?

What are other options for this patient?

A. Dietary and lifestyle changes? CGM to motivate?

B. Low-dose colchicine

C. EPA

D. GLP-1 agonist or SGLT2 inhibitor

Reference Here