Novel Lipid-Lowering therapies

From PROMINENT to HORIZON

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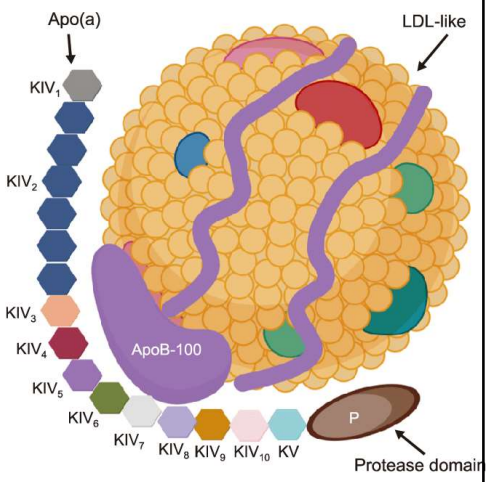

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Disclosures

Michael Blaha, M.D., faculty for this educational activity, is a consultant for Scene Health and Kowa; an adviser for Novartis, Novo Nordisk, Bayer, Eli Lilly, Merck, Amgen, Roche, AstraZeneca, Boehringer Ingelheim, Vectura and Agepha; and a speaker for Novo Nordisk. He receives grant and research support from the NIH, FDA, AHA, Bayer, Amgen and Novo Nordisk. He has indicated that the presentation or discussion will not include off-label or unapproved product usage.

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Learning Objectives

- Review Existing Lipid Lowering Guidelines
- Discuss New Concepts Using Existing Therapies
- Discuss the Latest Data on Non-Statin Lipid Lowering Therapies
  - Emphasis on **Pemafibrate** and the **PROMINENT** trial
  - Emphasis on **APO(a)-LRx , AKCEA-APO(a)-LRx , and TQJ230** and the **Lp(a) HORIZON** trial

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Talk Outline

- Current Guidelines for Lipid-Lowering Therapy
- Existing Lipid Lowering Therapies – New Concepts
- Bempedoic Acid
- Inclisiran
- Evinacumab
- Icosopent Ethyl (and other omega-3 preparations)
- Pemafibrate and the PROMINENT trial
- Emerging Therapies in Development
  - APO(a)-LRx , AKCEA-APO(a)-LRx , and TQJ230 and the Lp(a) HORIZON trial
  - TA-8995
  - Apo-CIII inhibition
  - Novel delivery of new therapies (including vaccines and gene editing)

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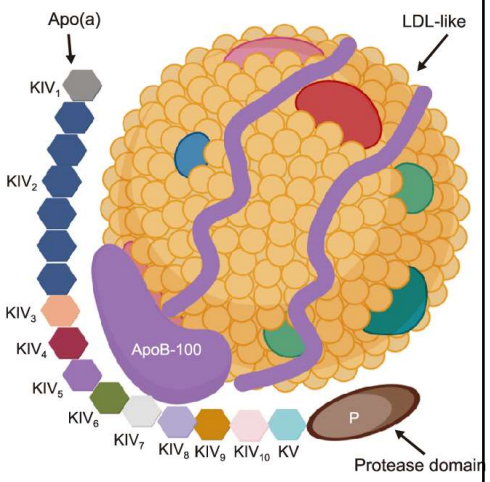
Clinical Guidelines

Part I



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New Clinical Guidelines (2º Prevention): LDL-C Lowering Based on CV Risk

2018 AHA/ACC Guidelines[1]

Very High-Risk ASCVD

Multiple major ASCVD events

ACS <12 months, history of MI (other than ACS event) or IS, symptomatic PAD

OR

1 major ASCVD event and multiple high-risk conditions

Age ≥65, heFH, history of CABG or PCI outside of major ASCVD events, DM, HTN, CKD, current smoker, persistently elevated LDL-C despite maximally tolerated statin therapy and ezetimibe, history of congestive HF

2019 ESC/EAS Guidelines[2]

Very High-Risk ASCVD

- **Documented ASCVD, including ACS*†‡**
- **DM with target organ damage**
- **Severe CKD**
- **A calculated SCORE ≥ 10%**
- **FH with ASCVD**

Statins are universally recommended as first-line therapy, followed by addition of ezetimibe and/or PCSK9i[1,2]

LDL-C THRESHOLD of 70 mg/dL[1]

Threshold = trigger to intensify therapy by using non-statin medications

LDL-C GOAL < 55 mg/dL AND ≥ 50% reduction from baseline[2]

Additionally, for ASCVD patients on maximally tolerated statin experiencing a **second vascular event within 2 years**, a lower **LDL-C goal of < 40 mg/dL** (< 1.0 mmol/L) may be considered

*MI or UA; †PCI, CABG, and other arterial revascularization procedures. ‡Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with 2 major epicardial arteries having > 50% stenosis), or on carotid ultrasound.·ABI, ankle brachial index, ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CT, computed tomography; DM, diabetes mellitus; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; FH, familial hypercholesterolemia; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary interventions; PCSK9, proprotein convertase subtilisin/kexin type 9; UA, unstable angina.

1. Grundy SM, et al. *J Am College Cardiol.* 2019;73:e285–e350. 2. Mach F, et al. *Eur Heart J.* 2020;41:111–188.

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Retrospective Cohort Study: Over 90% of Patients with Recent ACS Met the 2018 AHA/ACC Guideline Criteria for Very High Risk

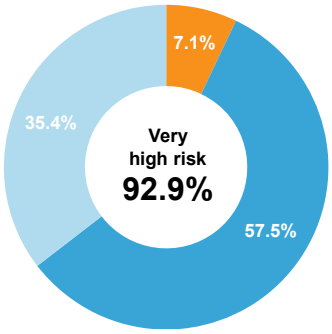
Patients:
US Adults with a history of a major ASCVD event in the MarketScan database (N = 16,344)

→ experienced an ACS in the past year (n = 3,626)

→ Followed from Jan 1, 2016-December 31, 2017 for recurrent ASCVD events

- A majority of patients were ≥65 years of age (54.5%) and had a prior PCI or CABG (51.2%) and diabetes mellitus (51.9%)
- HTN was the most common high-risk condition, present among 93.2% of patients
- 66.8% had an LDL-C ≥ 70 mg/dL

Patients With Recent Acute Coronary Syndrome



92.9% of all patients with a recent ACS met the Very High-Risk definition

- Not very high risk
- Very high risk: One major ASCVD event and multiple high-risk conditions
- Very high risk: Multiple major ASCVD events

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; VHR, very-h

Muntner P, et al. *Cardiovasc Drugs and Ther.* 2021:doi:10.1007/s10557-021-07167-1 ahead of print

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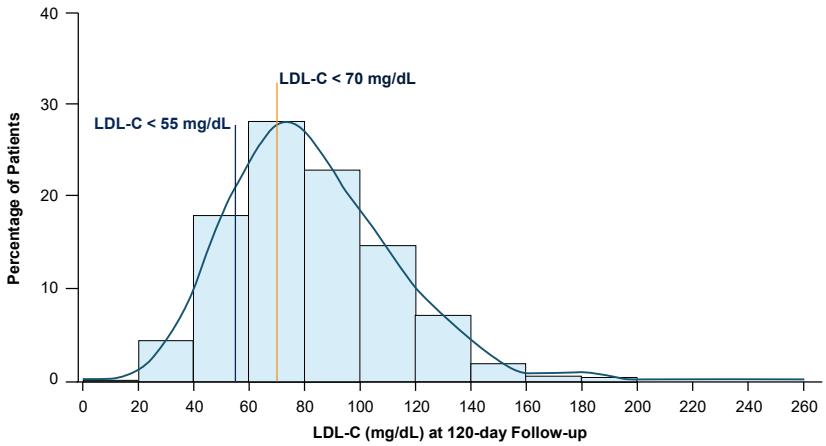
Fewer Than 40% of ACS Patients Achieve LDL-C < 70 mg/dL Even Fewer Achieve < 55 mg/dL at 120 Days Post-ACS

Multicenter, Observational Study: Dyslipidemia International Study (DYSIS) II: Patients from 18 Countries* with ACS

Patients:
N = 3,867
ACS cohort

Age:
62.3 ± 12.1 years

Distribution of LDL-C Levels at 120 Days Follow-up for the ACS Cohort



*Patients enrolled from 2012 to 2013 in Asia, Europe, and Middle East.
ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol
Gitt AK, *et al. Atherosclerosis.* 2017;266:158-166.

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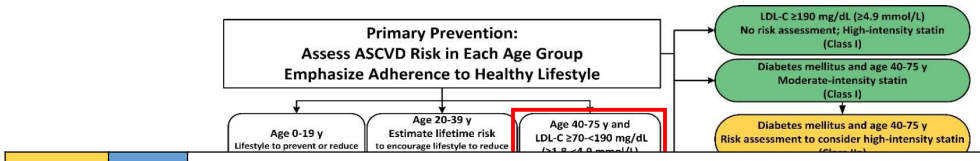
2018 ACC/AHA Cholesterol Guidelines: 1º Prevention



IIa	B-NR	In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone or initiate statin therapy.

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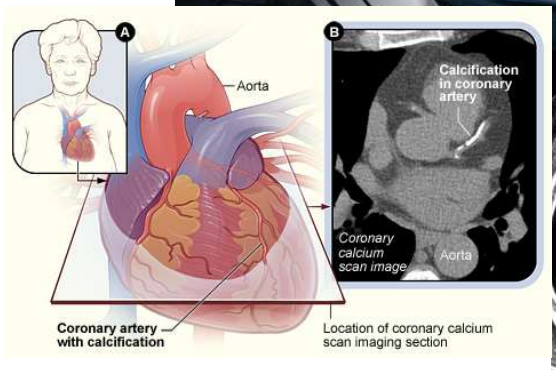

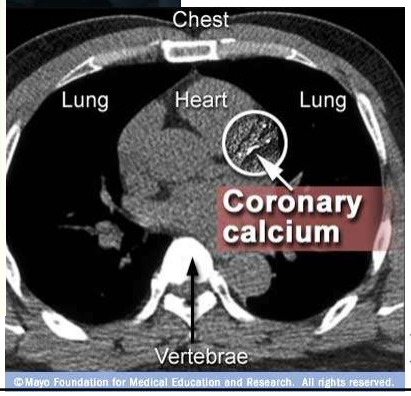

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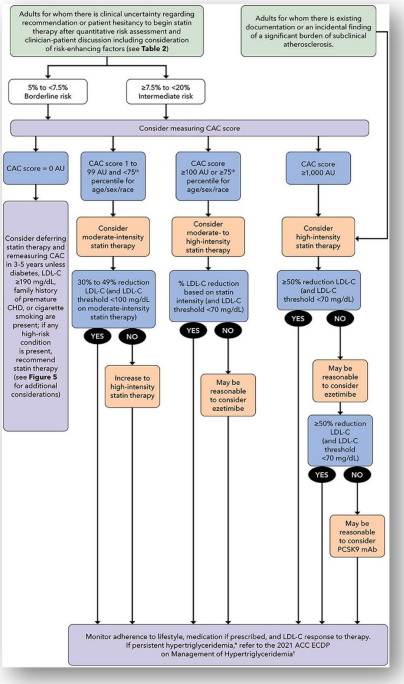

2022 ACC Expert Decision Consensus Pathway on Non-Statin Use

Writing Committee; Lloyd-Jones DM, et a. J Am Coll Cardiol. 2022 Oct 4;80(14):1366-1418.

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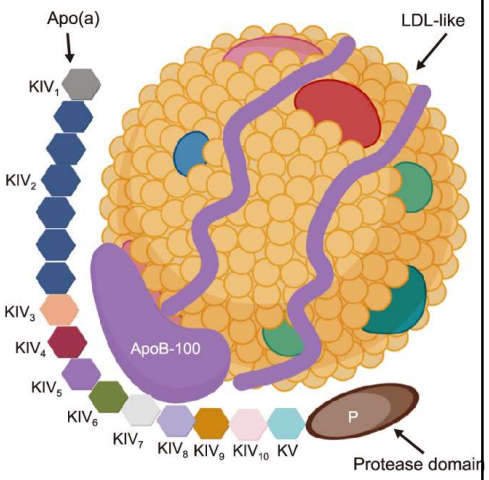
Existing Therapies – New Concepts:

Focus on Plaque and Early Treatment (ACS)

Part II



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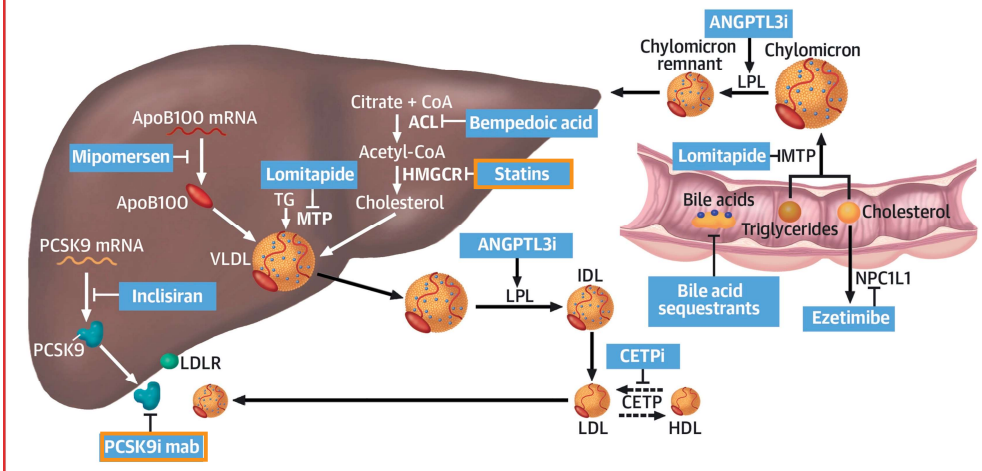
CENTRAL ILLUSTRATION: Working Mechanisms of Low-Density Lipoprotein Cholesterol Lowering Therapies



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

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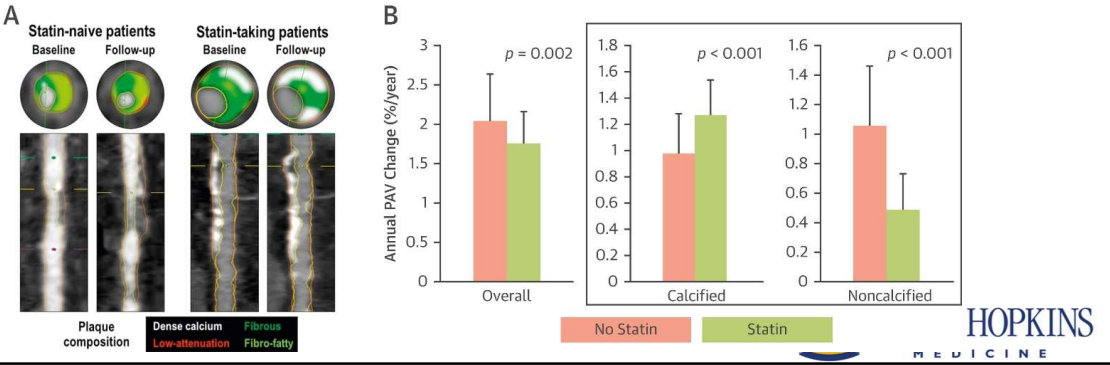
Effects of Statins on Coronary Atherosclerotic Plaques

The PARADIGM (Progression of AtheRosclerotic PlAque Determined by Computed TomoGraphic Angiography Imaging) Study

Sang-Eun Lee, MD, PhD,[a,b] Hyuk-Jae Chang, MD, PhD,[a,b] Ji Min Sung, PhD,[a,b] Hyung-Bok Park, MD,[b,c] Ran Heo, MD,[b,d] Asim Rizvi, MD,[e] Fay Y. Lin, MD,[e] Amit Kumar, MSc,[e] Martin Hadamitzky, MD,[f] Yong Jin Kim, MD, PhD,[g] Edoardo Conte, MD,[h] Daniele Andreini, MD, PhD,[h] Gianluca Pontone, MD, PhD,[h] Matthew J. Budoff, MD,[i] Ilan Gottlieb, MD, PhD,[j] Byoung Kwon Lee, MD, PhD,[k] Eun Ju Chun, MD, PhD,[l] Filippo Cademartiri, MD, PhD,[m] Erica Maffei, MD,[n] Hugo Marques, MD,[o] Jonathon A. Leipsic, MD,[p] Sanghoon Shin, MD,[q] Jung Hyun Choi, MD, PhD,[r] Kavitha Chinnaiyan, MD,[s] Gilbert Raff, MD,[s] Renu Virmani, MD,[t] Habib Samady, MD,[u] Peter H. Stone, MD,[v] Daniel S. Berman, MD,[w] Jagat Narula, MD, PhD,[x] Leslee J. Shaw, PhD,[u] Jeroen J. Bax, MD, PhD,[y] James K. Min, MD[e]



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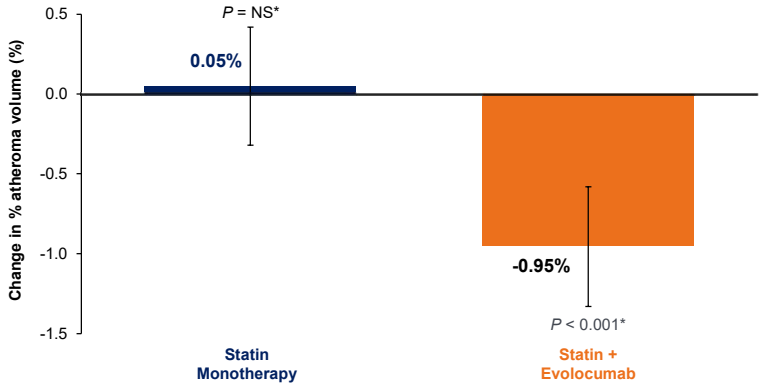
EVOLOCUMAB – GLAGOV Trial

Primary Endpoint: Nominal Change in PAV on IVUS From Baseline to Week 78



Mean change in coronary atherosclerotic plaque burden, as measured by Percent Atheroma Volume, from baseline to Week 78 (versus placebo) was -1.0% (-1.8, -0.64; P < 0.001)[1]

Data shown are least-squares mean (95% CI).
*Comparison versus baseline.
CI = confidence interval; NS = not significant; PAV = percent atheroma volume.
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.1695:.

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EVOLOCUMAB HUYGENS Trial: High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study

Aim: To evaluate the impact of PCSK9 inhibition with evolocumab on coronary atheroma phenotype post ACS

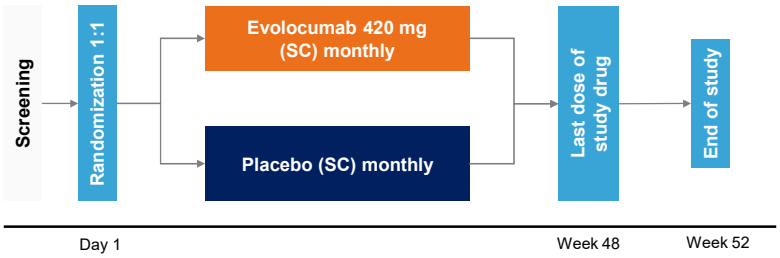
Eligibility Criteria:[1]

- NSTEMI
- Angiographic CAD
- LDL-C ≥60 mg/dL on high-intensity, ≥80 mg/dL on low/moderate-intensity or 130 mg/dL on no statin at screening
- Subsequently treated with maximally tolerated statin and
- Target segment on OCT containing ≥1 image with a FCT <120 µm and 1 image with lipid arc >90°

Study Endpoints:[1]

Primary: Absolute change in minimum FCT in a matched arterial segment from baseline to week 50.

Secondary: Percent change in minimum FCT, absolute change in the average of the minimum FCT for all images, absolute change in the maximum lipid arc.



164 patients met the eligibility criteria and were included in the study

This trial was not designed to assess a correlation between changes in FCT and CV events

CAD, coronary artery disease; FCT, fibrous cap thickness; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non-ST elevation myocardial infarction; OCT, optical coherenc
1. Nicholls SJ et al. *Cardiovasc Diagn Ther*. 2021;11:120-29.

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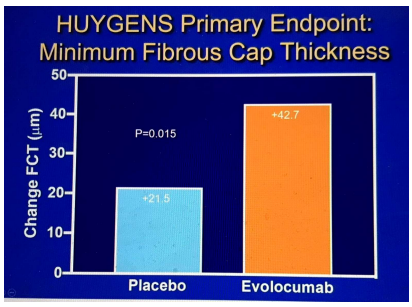
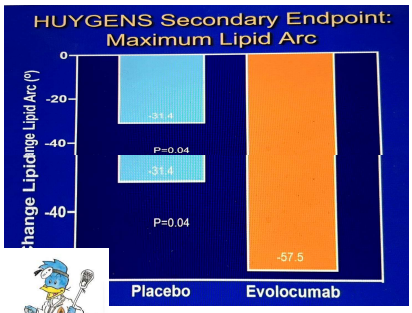
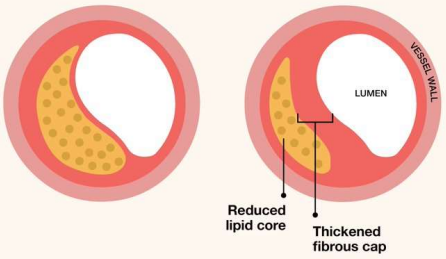




ESC
European Society of Cardiology

HUYGENS

Evolocumab and changes in plaque composition on OCT



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EVOLOCUMAB EVACS: A Double-Blind, 1:1 Randomized, Placebo-controlled Trial in Immediate ACS[1]

PRIMARY OBJECTIVE
Change in LDL-C at day 30[1]

SECONDARY OBJECTIVE
Change in other atherogenic lipoproteins[1]

Patients With ACS (N = 57)[1]

- All participants received high-intensity statins unless contraindicated and were treated per current ACS guidelines[1]
- Type 1 non-STEMI
- Troponin I ≥ 5 ng/mL

Screening → Randomization 1:1 → Evolocumab 420 mg (SC) / Placebo (SC) → End of Study

24 hours | Hospital discharge | 30-day follow-up

- A single dose of evolocumab added to a statin was administered within 24 hours of ACS hospitalization

:S trial was not designed to assess a correlation between LDL-C reduction and CV events

*The differences between the arms were controlled for in the statistical analysis.
ACS, acute coronary syndrome; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; SC, subcutaneous; STEMI, ST-elev
1. Leucker TM, et al. *Circulation*. 2020;142:419-421. 2. Leucker TM. Presented at: European Society of Cardiology. Aug 29-Sep 1, 2020.

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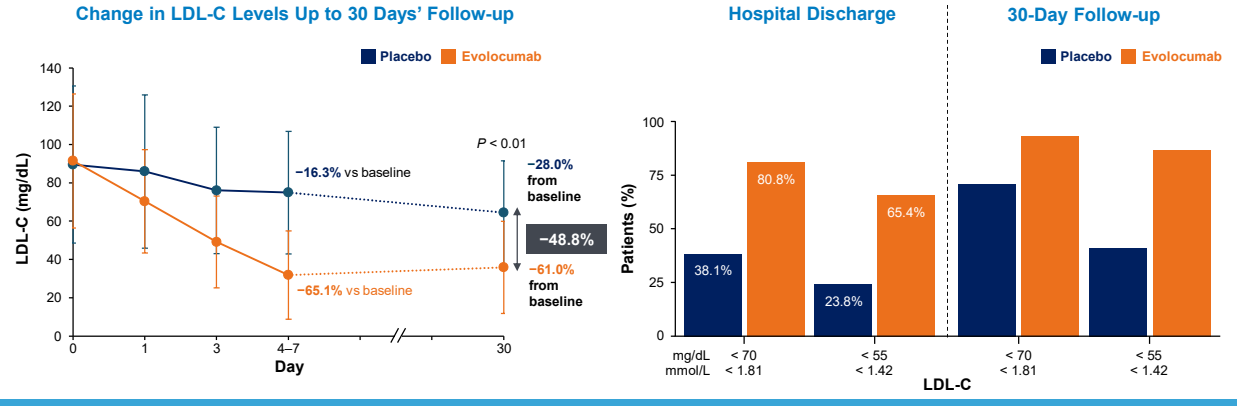
EVOLOCUMAB EVACS: Evolocumab, Added to Statin Therapy, Reduced LDL-C Levels at 30-day Follow-up



At 30-day follow-up, the percentage of evolocumab and placebo patients with any AE was (33% and 44%, respectively) and a serious AE was (7% and 22%, respectively)

The number of patients assessed at the different time points are as follows: baseline, 57 (evolocumab n = 30; placebo n = 27); day 1, 51 (evolocumab n = 26; placebo n = 25); day 3, 30 (evolocumab n = 16; placebo n = 14); day 4–7, 23 (evolocumab n = 15; placebo n = 8); day 30, 57 (evolocumab n = 30; placebo n = 27).

Data shown are mean reductions in LDL-C.

ACC, American College of Cardiology; AE, adverse event; AHA, American Heart Association; EAS, European Atherosclerosis Society; ESC, European Society of Cardiolo LDL-C, low-density lipoprotein cholesterol.

Leucker TM, et al. *Circulation*. 2020;142:419-421.

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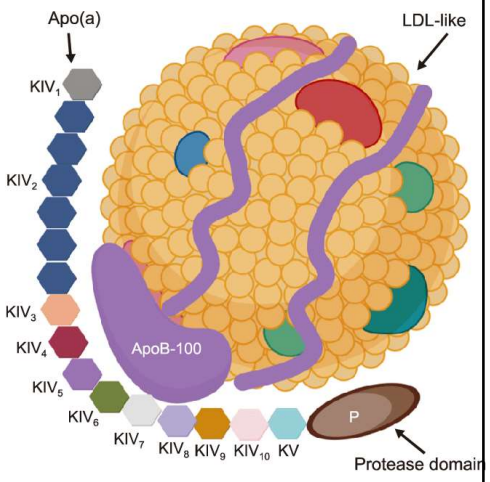
Bempedoic Acid

Part III



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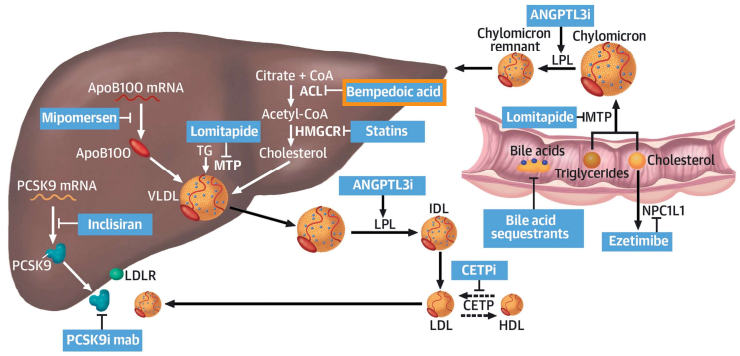
Bempedoic Acid

CENTRAL ILLUSTRATION: Working Mechanisms of Low-Density Lipoprotein Cholesterol Lowering Therapies



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

- Inhibits ATP-citrate lyase (ACL), enzyme upstream of HMG-CoA reductase inhibitor in the cholesterol synthesis pathway
- Prodrug activated in the liver
- Activated by ACSVL1, which is not present in muscle

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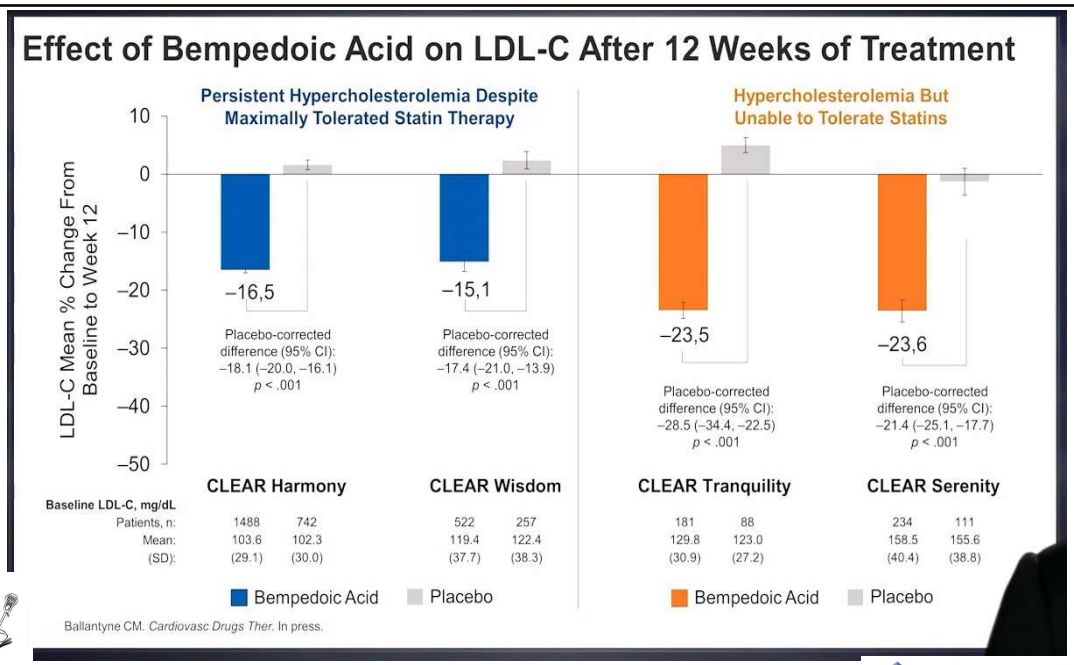
Effect of Bempedoic Acid on LDL-C After 12 Weeks of Treatment



Ballantyne CM. *Cardiovasc Drugs Ther.* In press.

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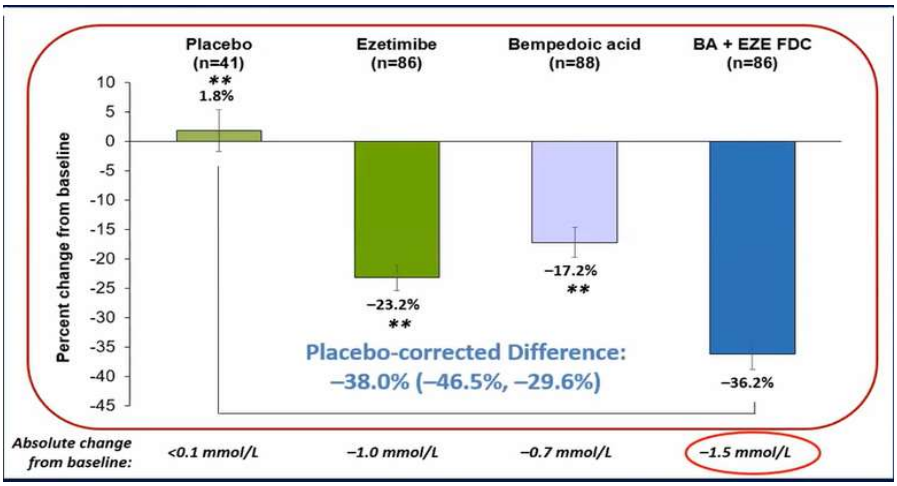
Percent Change From Baseline in LDL level at Week 12



Ballantyne CM et al. EJPC 2020

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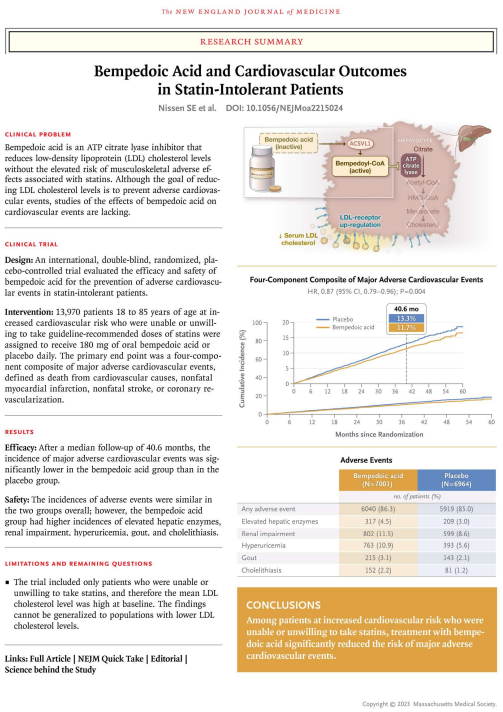

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

Nissen SE et al. DOI: 10.1056/NEJMoa2215024

CLINICAL PROBLEM

Bempedoic acid is an ATP citrate lyase inhibitor that reduces low-density lipoprotein (LDL) cholesterol levels without the elevated risk of musculoskeletal adverse effects associated with statins. Although the goal of reducing LDL cholesterol levels is to prevent adverse cardiovascular events, studies of the effects of bempedoic acid on cardiovascular events are lacking.

CLINICAL TRIAL

Design: An international, double-blind, randomized, placebo-controlled trial evaluated the efficacy and safety of bempedoic acid for the prevention of adverse cardiovascular events in statin-intolerant patients.

Intervention: 13,970 patients 18 to 85 years of age at increased cardiovascular risk who were unable or unwilling to take guideline-recommended doses of statins were assigned to receive 180 mg of oral bempedoic acid or placebo daily. The primary end point was a four-component composite of major adverse cardiovascular events, defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization.

RESULTS

Efficacy: After a median follow-up of 40.6 months, the incidence of major adverse cardiovascular events was significantly lower in the bempedoic acid group than in the placebo group.

Safety: The incidences of adverse events were similar in the two groups overall; however, the bempedoic acid group had higher incidences of elevated hepatic enzymes, renal impairment, hyperuricemia, gout, and cholelithiasis.

LIMITATIONS AND REMAINING QUESTIONS

- The trial included only patients who were unable or unwilling to take statins, and therefore the mean LDL cholesterol level was high at baseline. The findings cannot be generalized to populations with lower LDL cholesterol levels.

Links: Full Article | NEJM Quick Take | Editorial | Science behind the Study

Four-Component Composite of Major Adverse Cardiovascular Events

HR, 0.87 (95% CI, 0.79–0.96); P=0.004

Adverse Events

	Bempedoic acid (N=7001)	Placebo (N=6964)
	no. of patients (%)	
Any adverse event	6040 (86.3)	5919 (85.0)
Elevated hepatic enzymes	317 (4.5)	209 (3.0)
Renal impairment	802 (11.5)	599 (8.6)
Hyperuricemia	763 (10.9)	393 (5.6)
Gout	215 (3.1)	143 (2.1)
Cholelithiasis	152 (2.2)	81 (1.2)

CONCLUSIONS

Among patients at increased cardiovascular risk who were unable or unwilling to take statins, treatment with bempedoic acid significantly reduced the risk of major adverse cardiovascular events.

CLEAR OUTCOMES

Nissen SE, et al. N Engl J Med. 2023 Apr 13;388(15):1353-1364.

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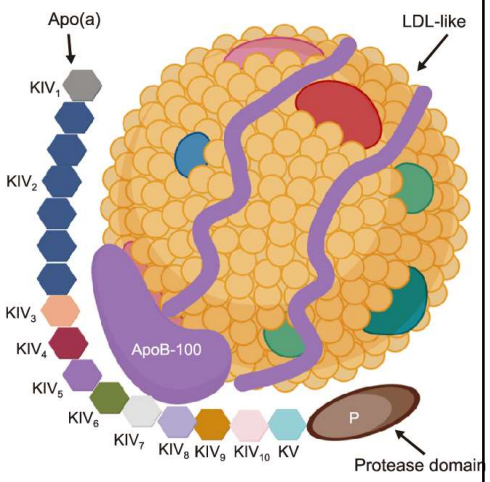
Inclisiran

Part IV



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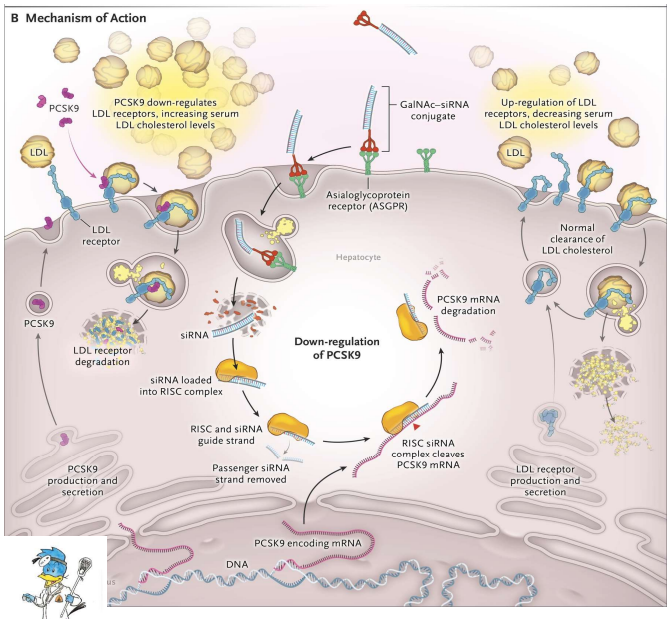

- Short-chain, synthetic, small interfering RNA (siRNA) that inhibits translation of PCSK9. Binds to the mRNA precursor, which then undergoes degradation.
- Proposed indication: Secondary prevention in patients with ASCVD and HeFH
- Administered: Subcutaneously with an initial dose followed by dosing at 3 months and then every 6 months thereafter.
- Inclisiran approved by EMA in Dec 2020, UK NICE in 2021, pending FDA approval

Rosenson RS et al. JACC 2018, Ray KK et al. NEJM 2020

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CENTRAL ILLUSTRATION: Inclisiran With Summary About Safety and Efficacy

Efficacy Favors Inclisiran

- Mean proprotein convertase subtilisin-kexin type 9 % change from baseline ↓80.9% at Day 510
- Mean LDL-C% change from baseline ↓50.7% at Day 510
- LDL-C level ↓55.1 mg/dL at Day 510

Pooled Data ORION-9, -10, -11

Twice a year dosing

Similar Safety to Placebo

- In this safety analysis: 3,655 patients with approximately 2,653 person years of exposure to inclisiran
- Similar safety profile between inclisiran and placebo
- Modest excess of self-limited mild-to-moderate TEAE at the injection site and bronchitis
- No difference between groups in liver, muscle, or hematological parameters

…it, R.S. et al. J Am Coll Cardiol. 2021;77(9):1182-93.

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HPS-4
TIMI 65
ORION-4

ORION-4 Design

Patients with stable atherosclerosis
(prior MI, prior stroke or PAD)

N~15,000

Lipid-lowering therapy optimized by primary provider

RANDOMIZE 1:1
DOUBLE BLIND

INCLISIRAN
300mg SC
(Randomization, M3, then q6M)

PLACEBO

Median duration of follow-up
4-5 years

Primary Endpoint: CHD death, MI, stroke or urgent coronary revasc

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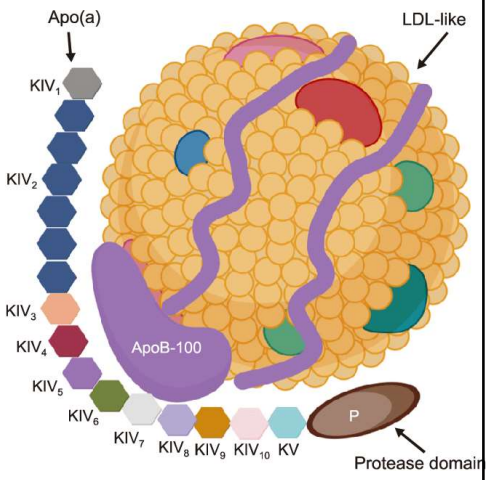
Evinacumab

Part V



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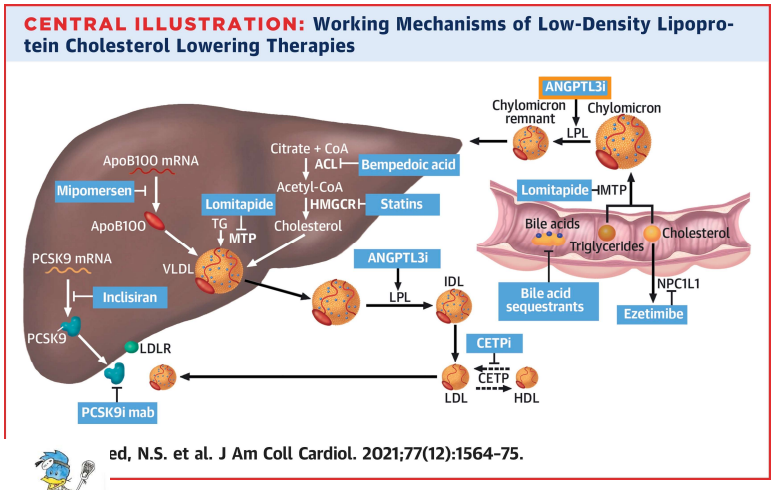
Evinacumab



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

- Angiopoietin-like 3 (ANGPTL3) is an inhibitor of lipoprotein lipase and endothelial lipase
- ANGPTL3 plays a key role in lipid metabolism by increasing levels of TGs and other lipids
- Loss-of-function variants in ANGPTL3 have been associated with low levels of both LDL-C and TGs
- Evinacumab is a fully human monoclonal antibody that is an inhibitor of ANGPTL3.

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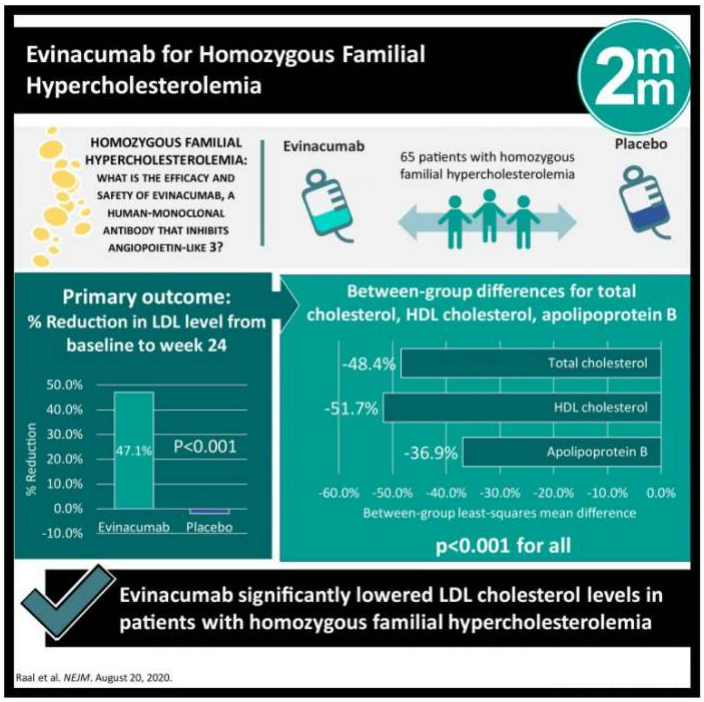

Raal F et al. NEJM 2020

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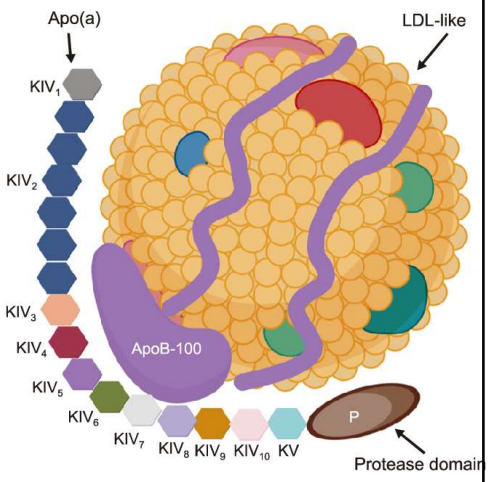
Icosapent Ethyl

Part VI



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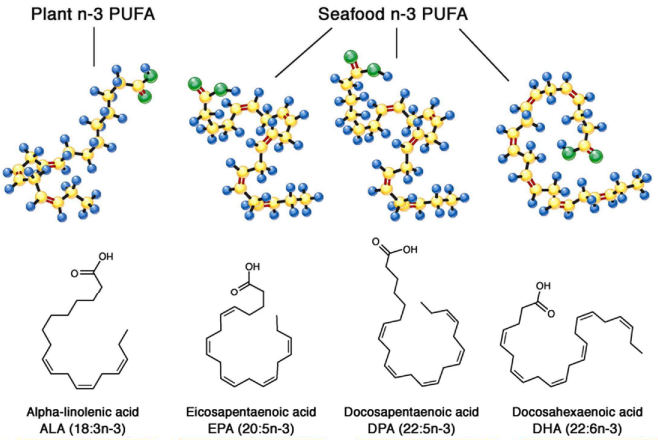
Omega-3 Fatty Acid



ffarian D et al. JACC 2011, Back M et al. FASEB 2019

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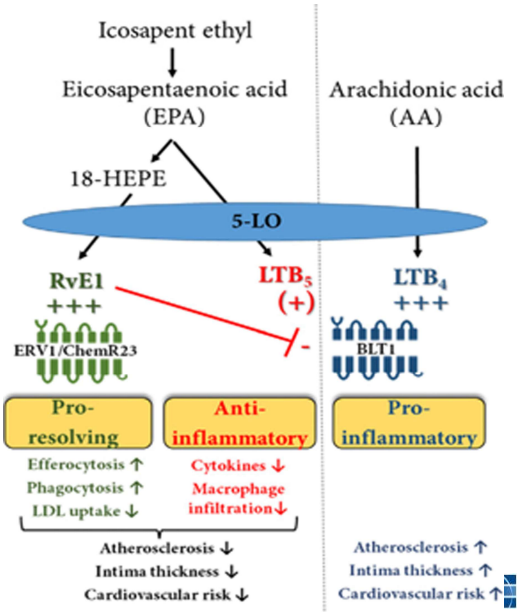

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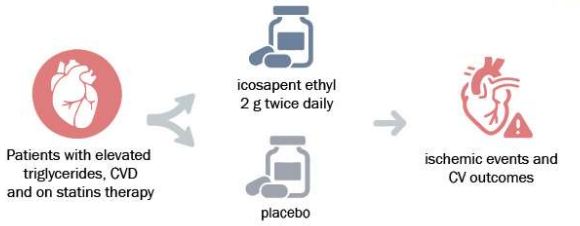
REDUCE IT: Cardiovascular Risk Reduction With Icosapent Ethyl for Hypertriglyceridemia

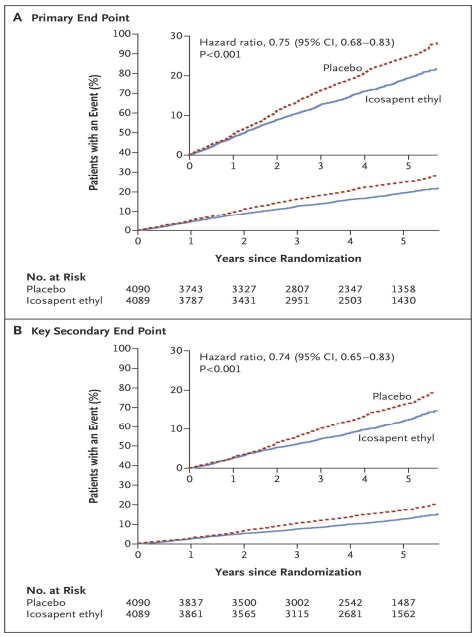
Multicenter, randomized, double-blind, placebo-controlled trial

AMERICAN COLLEGE of CARDIOLOGY



8,179 Patients with CVD or with diabetes and other risk factors, on statin therapy and elevated triglyceride levels (135-499 mg/dl) were randomized to

t DL, Steg G, Miller M et al. Cardiovascular risk reduction with icosapent ethyl for rtriglyceridemia: The REDUCE-IT trial. *NEJM* 2018;Nov 10:[Epub ahead of print].



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REDUCE-IT and STRENGTH- Similarities &Key Differences

	REDUCE-IT	STRENGTH
Active treatment	Icosapent ethyl 2 grams twice daily (EPA only)	Omega-3 carboxylic acid 4 grams daily (~2.2 grams EPA plus 0.8 grams DHA)
Placebo	Mineral oil	Corn oil
Follow-up, median (years)	4.9	3.5 (stopped early due to futility)
Primary end point	Composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, or unstable angina	Composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina
Event rates (%)	Icosapent ethyl: 17.2; mineral oil: 22 [HR: 0.75; 95% CI 0.68–0.83]	Omega-3 carboxylic acid: 12.0; corn oil: 12.2 [HR: 0.99; 95% CI 0.90–1.09]
EPA levels, change (%)	Icosapent ethyl: +393.5; mineral oil: 12.8 [serum]	Omega-3 carboxylic acid: +268.8; corn oil: 10.5 [plasma] Omega-3 carboxylic acid: +298.6; corn oil: 8.7 [RBC])

Virani SS et al. EHJCP 2021

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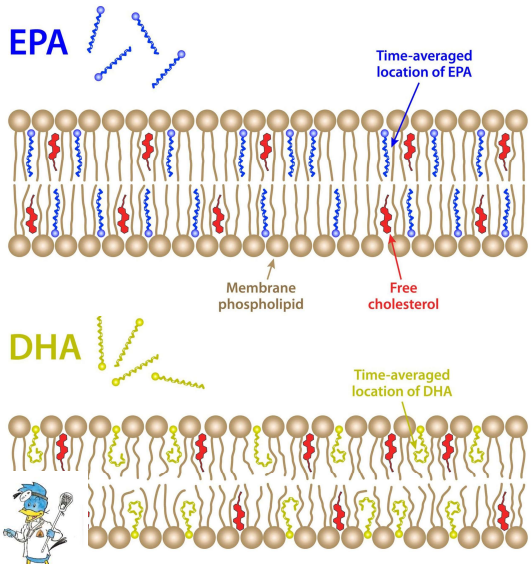
EPA vs DHA Mechanisms of Action?



EPA inhibits oxidation in different ApoB particles more than DHA.

EPA and DHA have different effects on membrane elasticity in the presence of high cholesterol.

Sherratt SCR et al. CPL 2018, Mason RP et al. JCP 2016.

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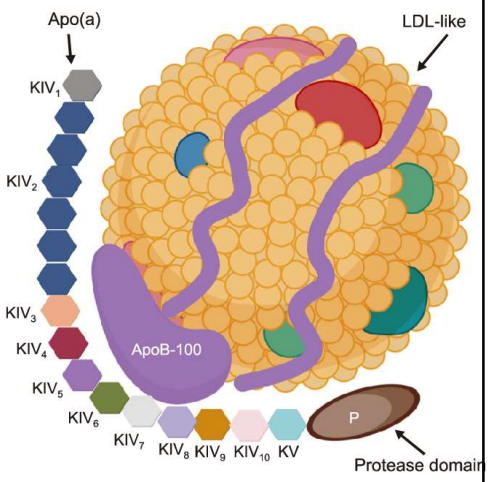
Pemafibrate and the PROMINENT trial

Part VII



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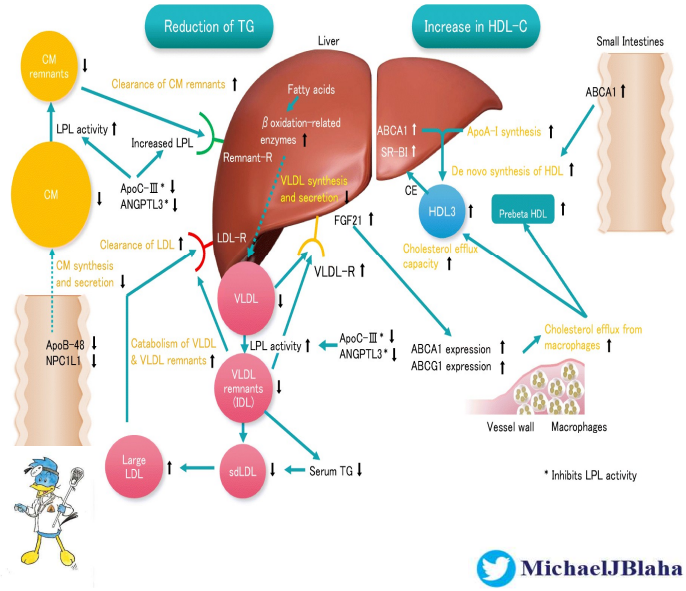
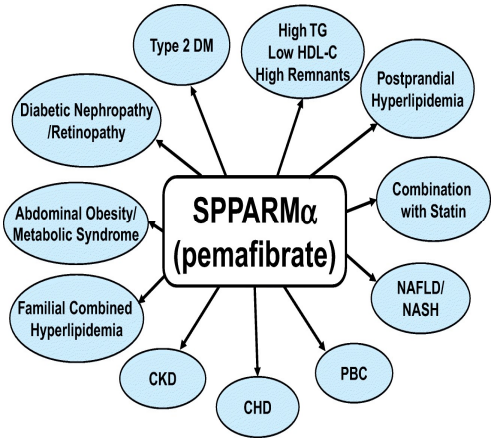
Pemafibrate





Yamashita S et al. Current Atherosclerosis Reports 2020

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PROMINENT Trial

MEN AND WOMEN WITH TYPE 2 DIABETES

10,000 PARTICIPANTS
24 Countries

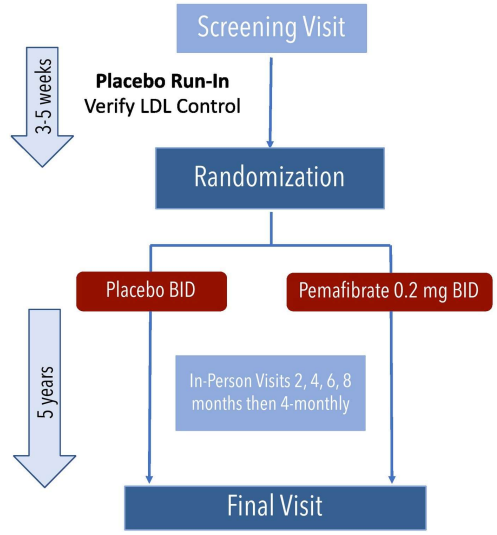
TG 200-499 mg/dl (2.26-5.64 mM) and HDL ≤ 40 mg/dl (1.03 mM)
Moderate-High Intensity Statin Therapy or LDL-C Control
(≤70 mg/dl other therapy or ≤100 mg/dl if statin intolerant)
1/3 Primary Prevention, 2/3 Secondary Prevention

ENDPOINTS

Event Driven: 1092 Primary Endpoints, 200 in ♀

PRIMARY ENDPOINT (MACE+):
Myocardial infarction, ischemic stroke, or unstable angina requiring unplanned revascularization, cardiovascular death.

Secondary/Tertiary Endpoints: all-cause mortality, any coronary revascularization, heart failure, total stroke, retinopathy, nephropathy, glycemic control, PAD, biomarkers, QOL



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2022

PROMINENT TRIAL

Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

Multinational, double-blind, randomized, controlled trial

Objective: To evaluate pemafibrate compared with placebo among patients with type 2 diabetes and hypertriglyceridemia.

10,497 Patients

Inclusion criteria:
Type 2 diabetes
Triglyceride level 200-499 mg/dL
High-density lipoprotein cholesterol (HDL-C) ≤40 mg/dL

pemafibrate 0.2 mg twice daily (n = 5,240) VS placebo (n = 5,257)

PRIMARY OUTCOME

3.6	CV death, nonfatal MI, ischemic stroke, or coronary revascularization % p = 0.67	3.5

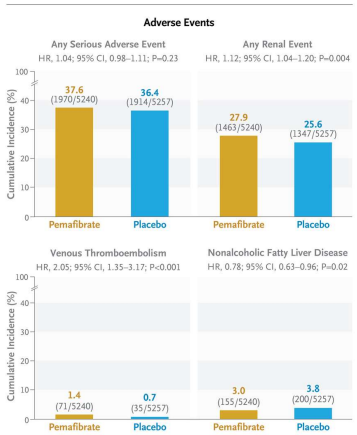
SECONDARY OUTCOMES

-31.1	Median change in triglyceride level from baseline %	-6.9
3.2	Median change in apolipoprotein B level from baseline %	-1.6
10.7	Any adverse renal event p = 0.004	9.6

Conclusion: Among patients with type 2 diabetes, mild-to-moderate hypertriglyceridemia, and low HDL and LDL cholesterol levels, the incidence of cardiovascular events was not lower among those who received pemafibrate than among those who received placebo, although pemafibrate lowered triglyceride, VLDL cholesterol, remnant cholesterol, and apolipoprotein C-III levels.

Aruna Das Pradhan et al. NEJM, 2022; 387:1923-1934

Visualmed



LIMITATIONS AND REMAINING QUESTIONS

- The findings cannot exclude the possibility that increases in apolipoprotein B and LDL cholesterol levels in the pemafibrate group negated any benefit of reduction of triglyceride levels.
- The data are consistent with increased efficiency in conversion of triglyceride-rich lipoprotein remnants to LDL rather than their removal by the liver; ongoing trials of agents that use alternative pathways to lower levels of triglycerides and remnant particles may clarify whether clearance of these remnants is required for cardiovascular benefit.

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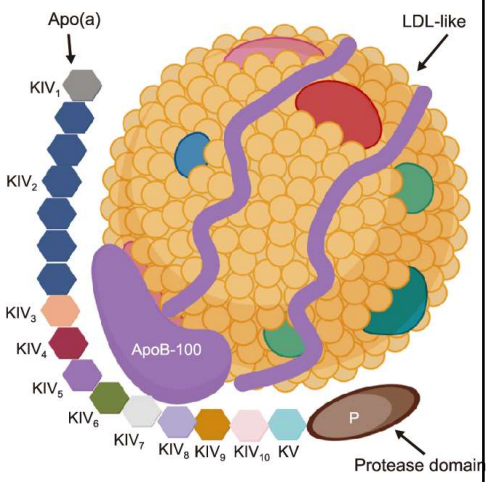
Emerging Therapies

Part VIII



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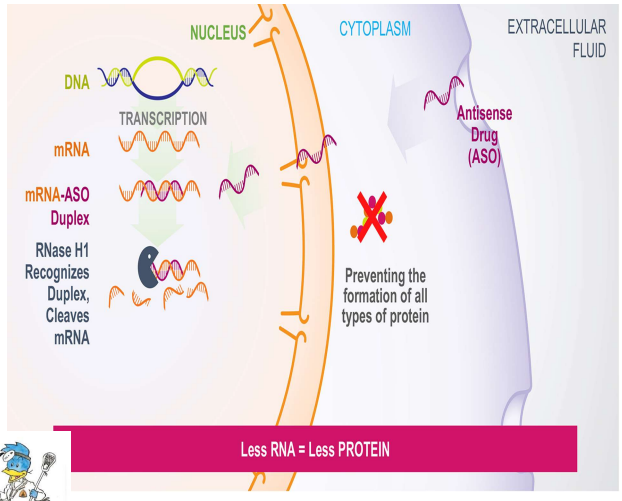
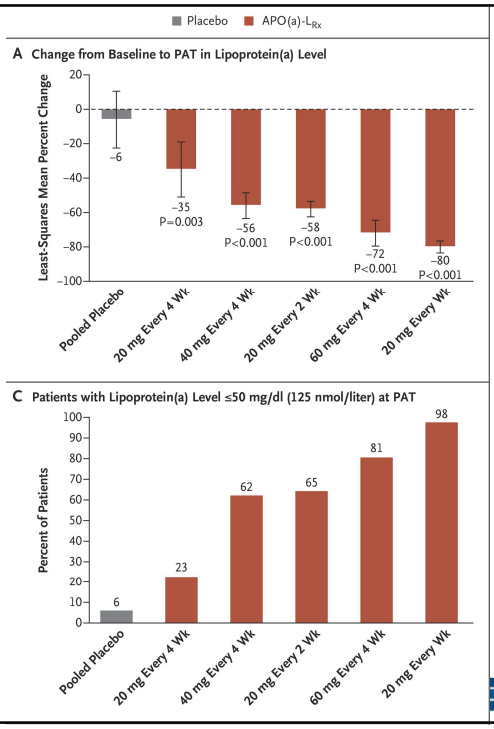
APO(a)-LRx , AKCEA-APO(a)-LRx, and TQJ230 (antisense oligonucleotide)





Tsimikas S et al. JACC 2021
Tsimikas S et al. NEJM 2020

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PELICARSEN

Lp(a) Horizon
Outcomes Study

- **Phase 3 pivotal CVOT**
- **Randomized double-blind, placebo-controlled multicenter trial**
- **7,680 individuals**
- **Lp(a) >70 mg/dL**
- **MI or ischemic stroke between 3 months and 10 years prior, or PAD**
- **Optimal LDL lowering and risk factor control at randomization**
- ~4.25 year mean follow-up
- Anticipating about 993 events
- Expanded MACE (CV death, MI, stroke, urgent coronary revascularization)
- Prespecified analysis in Lp(a) >90 mg/dL

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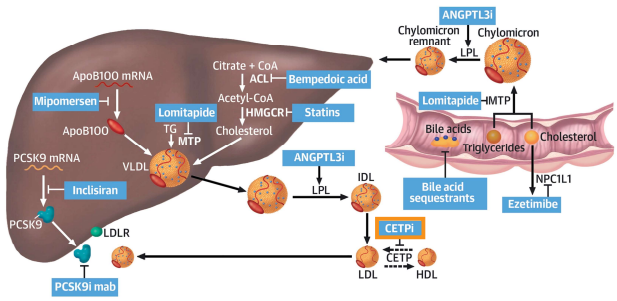
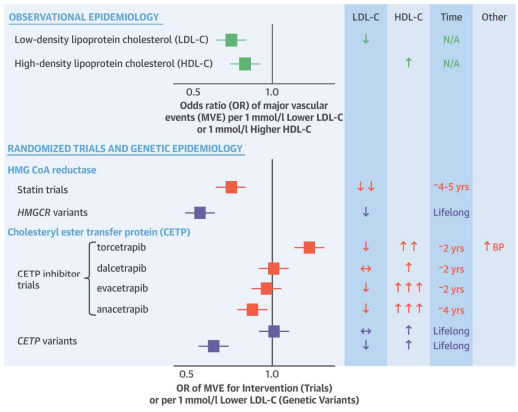
Obicetrapib (CETP Inhibitor)

CENTRAL ILLUSTRATION: Working Mechanisms of Low-Density Lipoprotein Cholesterol Lowering Therapies



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

CENTRAL ILLUSTRATION: Effects of Cholesteryl Ester Transfer Protein Inhibitors and Genetic Variants on Major Cardiovascular Outcomes in the Context of Relevant Observational Epidemiology and Statin Therapy



Armitage, J. et al. J Am Coll Cardiol. 2019;73(4):477-87.

TA-8995 lowers LDL-C by 45%

Larsen L et al. ATVB 2019

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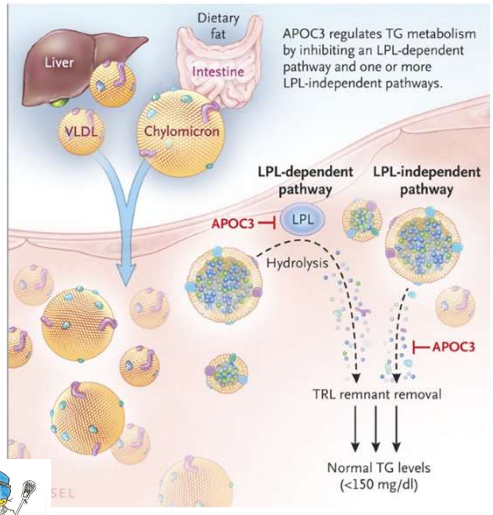
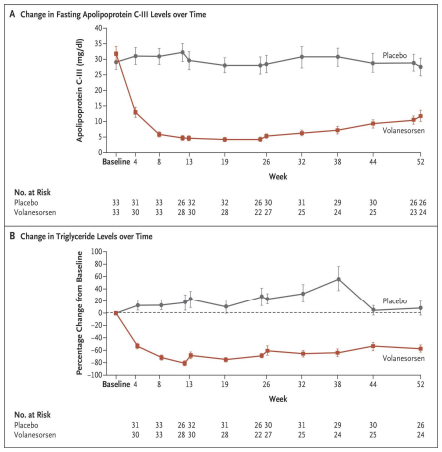
Apo-CIII Inhibitors



Gaudet D et al. NEJM 2014

Volanesorsen



Witztum J et al. NEJM 2019

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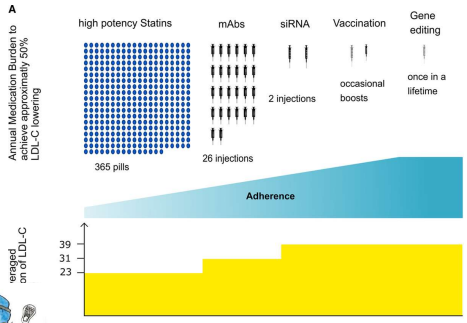
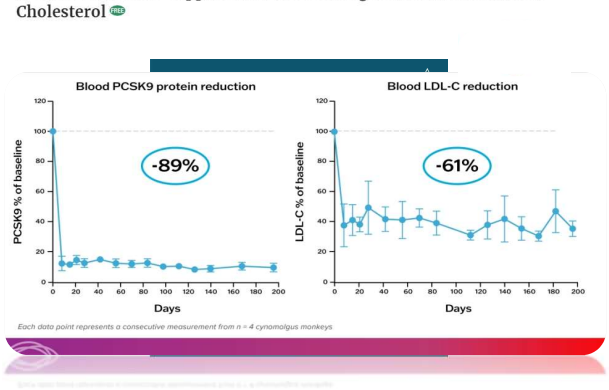
New Drug Delivery Strategies

- Oral PCSK9i, combined with other mechanisms?
- SQ ANGPTL3 (vupanorsen)
- "Vaccines"and Gene Editing



Brandts J et al. Circulation 2021



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Take Home Messages and Next Steps

- Lipid Guidelines are pushing for:
  - More personalization
  - More aggressive LDL goals (<55 mg/dL in many)
  - Earlier treatment including potentially during ACS admission
- Many non-Statin therapy options now – almost anyone can achieve lipid goals if desired and adherent to therapy
- Pemafibrate – failed CVOT, very little role for fibrates in 2024
- APO(a)-LRx , AKCEA-APO(a)-LRx , and TQJ230 – CVOT to result in 2025, may be most impactful new therapy in years

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QUESTIONS

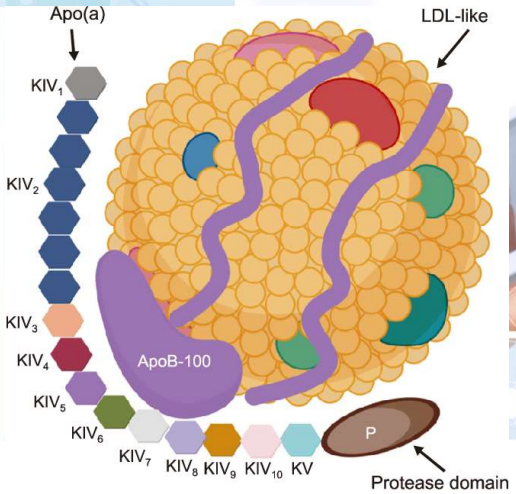

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TABLE 1 Discussed Available and Novel LDL-C-Lowering Therapies

Name	Drug Target	Phase	Effect on LDL-C
Statins	HMGCR	Approved	20% to 50%
Ezetimibe	NPC1L1	Approved	~23%
PCSK9i antibody	PCSK9	Approved	~47%
Mipomersen	ApoB100 mRNA	Approved, FDA only	26%
Lomitapide	MTP	Approved, with registry	40% to 50%
Bempedoic acid	ACL	Approved/phase 4	17% to 21%
Inclisiran	PCSK9 mRNA	Phase 3	~50%
Evinacumab	ANGPTL3	Phase 3	~49%
AKCEA-ANGPTL3-L_{Rx}	ANGPTL3 mRNA	Phase 2	~33%
ARO-ANG3	ANGPTL3 mRNA	Phase 1	Up to 42%
TA-8995	CETP	Phase 2	Up to 45%

Nurmohamed N et al. JACC 2021

CEU 2021

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References

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2.Mach, F., et al. (2020). Eur Heart J, 41, 111–188.
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6.Gitt, A. K., et al. (2017). Atherosclerosis, 266, 158-166.
7.Mozaffarian, D., et al. (2011). JACC.
8.Back, M., et al. (2019). FASEB.

CEU 2021

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