The Lipid Landscape: Exploring Non-Statin Pathways

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03/04/2026

Disclosures and Acknowledgements

- The planner(s) and speaker(s) have indicated that there are no relevant financial relationships with any ineligible companies to disclose.
- Special thank you to:
  - Andrew Clark, PharmD, BCPS, CDCES, CPP
  - Rachel Long, PharmD, BCPS, CDCES, CPP
  - Kayla Marvin, PharmD, BCACP, CDCES, CPP
  - Kristen McKnight, PharmD, BCPS, CDCES, CPP
  - Elaine R. Thomas, PharmD, BCPS, BCGP, MHA

Learning Objectives

At the end of this session, learners should be able to:

- Outline recent clinical trial evidence and guideline updates informing the use of non-statin therapies for ASCVD risk reduction
- Compare the mechanisms of action, lipid-lowering efficacy, and key clinical differences among current non-statin lipid-lowering therapies
- Classify the appropriateness of non-statin lipid-lowering therapy based on patient characteristics and clinical evidence
- Apply evidence-based strategies to select, initiate, and monitor non-statin lipid-lowering therapies in clinical practice

Abbreviation Key

Abbreviation	Meaning
ABI	Ankle-Brachial Index
ACS	Acute Coronary Syndrome
ACC	American College of Cardiology
ACL	ATP-Citrate Lyase
AHA	American Heart Association
ANGPTL3	Angiopoietin-Like Protein 3
ASCVD	Atherosclerotic Cardiovascular Disease
BAS	Bile Acid Sequestrants
CAC	Coronary Artery Calcium
CKD	Chronic Kidney Disease
DHA	Docosahexaenoic Acid
eGFR	Estimated Glomerular Filtration Rate
EPA	Eicosapentaenoic Acid
FeFH / HeFH	Heterozygous Familial Hypercholesterolemia
FoFH / HoFH	Homozygous Familial Hypercholesterolemia
HDL	High-Density Lipoprotein
HF	Heart Failure
HTN	Hypertension
LAD	Left Anterior Descending Artery
LFTs	Liver Function Tests
LDL-C	Low-Density Lipoprotein Cholesterol
Lp(a)	Lipoprotein(a)

Abbreviation	Meaning
LPL	Lipoprotein Lipase
MACE-4	Major Adverse Cardiovascular Events (4-component composite)
MI	Myocardial Infarction
MOA	Mechanism of Action
MTP	Microsomal Triglyceride Transfer Protein
NLA	National Lipid Association
NPC1L1	Niemann-Pick C1-Like 1
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
PPAR-α	Peroxisome Proliferator–Activated Receptor Alpha
RCA	Right Coronary Artery
siRNA	Small Interfering RNA
STEMI	ST-Elevation Myocardial Infarction
TC	Total Cholesterol
TG	Triglycerides
ULN	Upper Limit of Normal
VLDL	Very Low-Density Lipoprotein

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Brief Note on Statin Therapy

- Statins remain the cornerstone of lipid management for most indications.
- Statins are well-studied with a long record of safety and evidence in improving outcomes.
- However, some patients may not be able to tolerate statins due to side effects including muscle aches/pains, etc.
- Some patients need other lipid-lowering therapies in addition to max tolerated statins to achieve lipid goals and reduce CV risk

Intensity	Statins (Daily Dose)	LDL-C ↓
High	Atorvastatin 40–80 mg Rosuvastatin 20–40 mg	≥50%
Moderate	Atorvastatin 10–20 mg Rosuvastatin 5–10 mg Simvastatin 20–40 mg Pravastatin 40–80 mg Pitavastatin 2–4 mg	30–49%
Low	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Pitavastatin 1 mg	<30%

ADVOCATE HEALTH

Michos ED, McEvoy JW, Blumenthal RS. Lipid management for the prevention of atherosclerotic cardiovascular disease. *N Engl J Med*. 2019;381(16):1557-1567. doi:10.1056/NEJMra1806939

2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering

ADVOCATE HEALTH

Purpose

- To answer the following questions:
  - Who should use the newer non-statin therapies?
  - Which newer therapies should be used in patients who are statin intolerant and when should they be used?
  - What order should newer medications be added?
- Breaks down recommendations into algorithms based on risk
- Emphasizes that percentage LDL lowering has a higher predictive value of statin benefit compared to achieved LDL level

ADVOCATE HEALTH

Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 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. J Am Coll Cardiol. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

Criteria for Defining Patients at Very High Risk of Future ASCVD Events

High-Risk Conditions
Age ≥65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

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 PAD (history of claudication with ABI <0.85 or previous revascularization or amputation)

**Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

ADVOCATE HEALTH

Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 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. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

Lipoprotein (a)

- Lp(a) is an independent and causal risk factor for ASCVD, promoting thrombosis, atherosclerosis, and valvular aortic stenosis
- High risk defined as ≥ 100 or ≥ 125 nmol/L recommended by NLA and ACC/AHA, respectively
- Consideration of race/ethnic variations in Lp(a) expression
- Testing reasonable in adults with a personal or family history of premature ASCVD or FH or to refine risk assessment in those at borderline (5%-7.4%) ASCVD risk

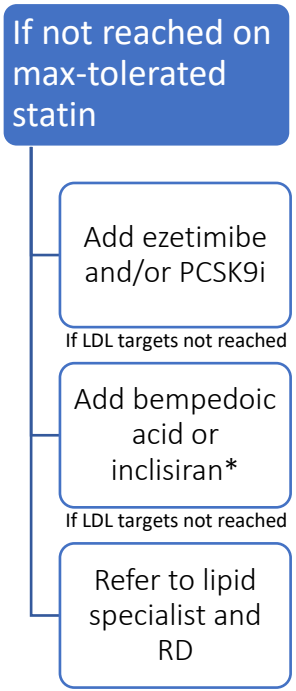
ADVOCATE HEALTH

Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 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. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

Very High Risk ASCVD

Target ≥50% LDL reduction **and** LDL <55 mg/dL

(Secondary Prevention)



*inclisiran in place of PCSK9i

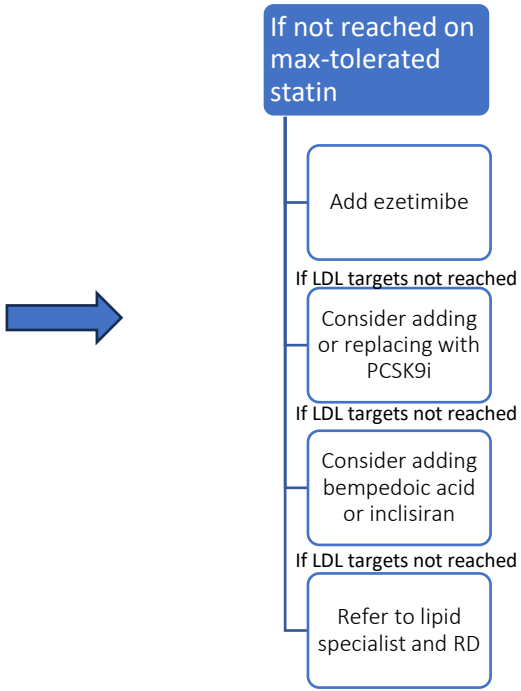
ADVOCATE HEALTH

Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 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. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

Not at Very High Risk ASCVD

Target ≥50% LDL reduction **and** LDL <70 mg/dL

(Secondary Prevention)



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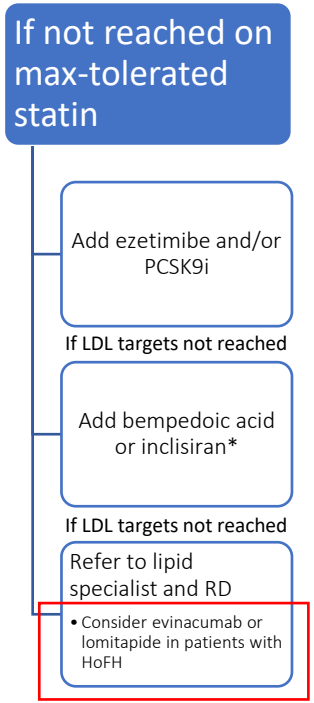
Baseline LDL ≥190 mg/dL with ASCVD

without clinical/genetic FH diagnosis

Target ≥50% LDL reduction **and** LDL <70 mg/dL

(Secondary Prevention)



with clinical/genetic FH diagnosis

Target ≥50% LDL reduction **and** LDL <55 mg/dL

(Secondary Prevention)

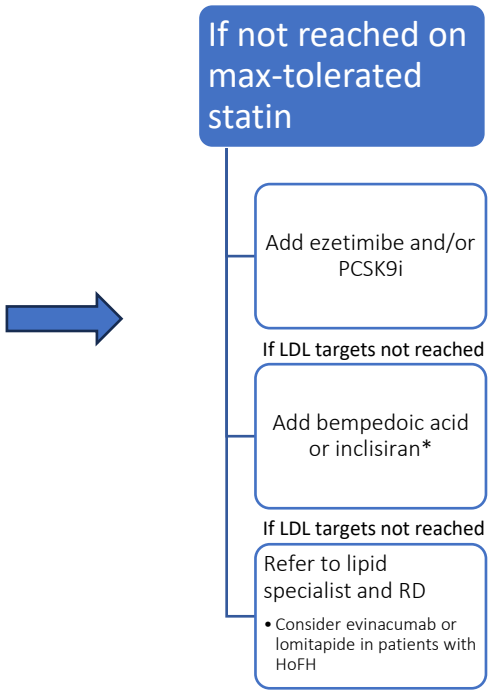
ADVOCATE HEALTH

Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 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. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

Baseline LDL ≥190 mg/dL without ASCVD

Target ≥50% LDL reduction **and** LDL <100 mg/dL

(Secondary Prevention)



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Adults with diabetes (LDL <190 mg/dL)

Ages 40 - 75

Target ≥50% LDL reduction and LDL <100 mg/dL

If 10-yr ASCVD Risk ≥20%: Target ≥50% LDL reduction and LDL <70 mg/dL

(Primary Prevention)

10-year ASCVD risk ≥7.5%, diabetes-specific risk enhancers or subclinical atherosclerosis (on max tolerated statin)

- Consider adding ezetimibe
- May consider bile acid sequestrant if fasting TG <300 mg/dL

ADVOCATE HEALTH

Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 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. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

Adults without diabetes (LDL 70-189 mg/dL)

Ages 40 - 75

If 10-yr ASCVD Risk ≥20%:
Target ≥50% LDL reduction and LDL <70 mg/dL

(Primary Prevention)

If not reached on max-tolerated statin

Consider ezetimibe

ADVOCATE HEALTH

Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 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. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients with Persistent Hypertriglyceridemia

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Primary Prevention Patients with Triglycerides 150-500 mg/dL

- The ACC emphasizes there is limited randomized controlled trial evidence demonstrating ASCVD risk reduction with triglyceride risk-based nonstatin therapies in primary prevention patients without diabetes
- The pathway recommends shared decision-making and consideration of patient preferences regarding the addition of triglyceride risk-based nonstatin therapy in this population

ADVOCATE HEALTH

Virani SS, Morris PB, Agarwala A, et al. 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;78(9):960-993. doi:10.1016/j.jacc.2021.06.011

Severe Hypertriglyceridemia (≥500 mg/dL)

- For patients with triglycerides ≥500 mg/dL, the ACC recommends prescription omega-3 fatty acids (icosapent ethyl or omega-3 acid ethyl esters) if triglycerides remain persistently elevated or increasing
- Consider fibrate therapy if necessary to prevent acute pancreatitis

ADVOCATE HEALTH

Virani SS, Morris PB, Agarwala A, et al. 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;78(9):960-993. doi:10.1016/j.jacc.2021.06.011

Assessment Question #1

A 40-year-old man with premature ASCVD has a lifelong history of severely elevated LDL-C levels (>400 mg/dL untreated). Genetic testing confirms HoFH. Despite maximally tolerated statin therapy, ezetimibe, and a PCSK9 inhibitor, his LDL-C remains markedly above goal. Which of the following is the most appropriate next step?

A. Add bempedoic acid or inclisiran before referral

B. Intensify statin therapy to achieve ≥50% LDL-C reduction

C. Refer to a lipid specialist and consider evinacumab or lomitapide

D. Continue current therapy because PCSK9 inhibitors are maximal therapy

Non-Statin Therapies and Relevant Clinical Trial Data

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Bempedoic Acid

- Bempedoic acid is an adenosine triphosphate-citrate lyase (ACL) inhibitor that blocks cholesterol synthesis in the liver, thereby lowering low-density lipoprotein cholesterol (LDL-C) level in blood.
  - ACL is an enzyme that catalyzes the conversion of citrate to acetyl CoA. This is a process involved in the cholesterol synthesis pathway, upstream of HMG-CoA reductase

ADVOCATE HEALTH

Bempedoic Acid. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.

Bempedoic Acid (cont.)

- Dosing:
  - Form: tablet
  - 180 mg by mouth once daily with or without food
- Most common side effects:
  - Upper respiratory tract infection (4.5%), muscle spasms (3.6%), hyperuricemia (3.5%), back pain (3.3%), abdominal pain or discomfort (3.1%), bronchitis (3.0%), pain in extremity (3.0%), anemia (2.8%), and elevated liver enzymes (2.1%)
- Clinical Impact:
  - LDL effect: ↓ 15-20% (~30% w/ ezetimibe)
  - TG effect: ↓ 5-10%

ADVOCATE HEALTH

Bempedoic Acid. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.

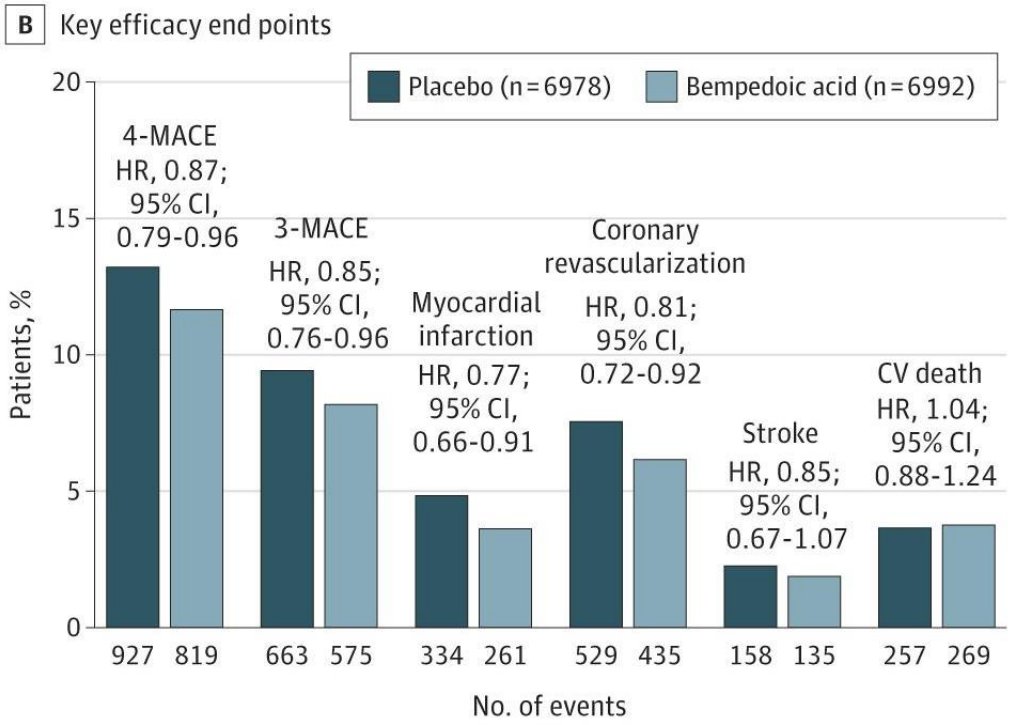
Bempedoic Acid: CLEAR Outcomes Trial

- Randomized, double-blind trial of 13,970 statin-intolerant patients with established or high-risk ASCVD and LDL ≥100 mg/dL.
- Compared bempedoic acid 180 mg daily vs placebo.
- Primary endpoint: MACE-4 (CV death, nonfatal MI, nonfatal stroke, or coronary revascularization).
- At 6 months: LDL-C ↓ 21% and hs-CRP ↓ 22%.
- Median follow-up: 3.4 years.

ADVOCATE HEALTH

Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. *N Engl J Med*. 2023;388(15):1353-1364. doi:10.1056/NEJMoa2215024

CLEAR Outcomes Trial: Endpoints



The trial met its primary endpoint, with bempedoic acid reducing MACE-4 by 13% compared to placebo (HR 0.87, 95% CI 0.79-0.96)

ADVOCATE HEALTH

Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. *N Engl J Med*. 2023;388(15):1353-1364. doi:10.1056/NEJMoa2215024

Omega-3 Fatty Acids

- Icosapent ethyl (EPA), omega-3 acid ethyl esters (EPA+DHA)
- Potential mechanisms of action include decreased hepatic lipogenesis and increased plasma lipoprotein lipase activity.
- Icosapent ethyl is a prescription strength product with clinical trial data (versus OTC omega-3 fatty acids)

ADVOCATE HEALTH

Icosapent Ethyl. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.
Omega-3 Fatty Acids. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.

Omega-3 Fatty Acids (cont.)

- Dosing:
  - Form: capsule
  - Icosapent Ethyl/omega-3 acid ethyl esters: 4 grams by mouth once daily (or 2 grams twice daily) with food
- Most common side effects:
  - Eructation (belching) (4%), dyspepsia (3%), and taste perversion (4%)
- Clinical Impact:
  - LDL effect: neutral/↓ with icosapent ethyl, neutral/↑ with omega-3 acid ethyl esters
  - TG effect: ↓ 20-50%

ADVOCATE HEALTH

Icosapent Ethyl. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.
Omega-3 Fatty Acids. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.

Icosapent Ethyl: REDUCE-IT Trial

- Multinational, randomized, double-blind, placebo-controlled trial of 8,179 statin-treated patients with controlled LDL-C but elevated TG.
- Baseline levels: LDL-C 41–100 mg/dL (median 75) and TG 135–499 mg/dL (median 216).
- Compared Icosapent ethyl 2 g BID (4 g/day) vs mineral oil placebo.
- Median follow-up: 4.9 years.

ADVOCATE HEALTH

Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22. doi:10.1056/NEJMoa1812792

REDUCE-IT Trial: Endpoints

- Primary composite endpoint (CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina):
  - 17.2% with icosapent ethyl vs 22.0% with placebo (HR 0.75, 95% CI 0.68–0.83).
- U.S. subgroup showed greater benefit:
  - 18.2% vs 24.7% (HR 0.69, P=0.000001).
- All-cause mortality reduced in U.S. patients:
  - 7.2% vs 9.8% (HR 0.70, P=0.004).

ADVOCATE HEALTH

Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22. doi:10.1056/NEJMoa1812792

REDUCE-IT Trial: Lipid Effects

Median Change %	Icosapent Ethyl	Placebo
TG	-18.3% (-39.0 mg/dL)	2.2 (4.5 mg/dL)
LDL	3.1% (2.0 mg/dL)	10.2% (7.0 mg/dL)

- However, the cardiovascular benefit appears to exceed what would be expected from lipid lowering alone
  - Baseline triglyceride levels (≥150 vs. <150 mg/dL had no influence on the primary or key secondary efficacy end points

ADVOCATE HEALTH

Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22. doi:10.1056/NEJMoa1812792

Evolocumab/Alirocumab

- Evolocumab/Alirocumab is a human monoclonal antibody that binds to proprotein convertase subtilisin kexin type 9 (PCSK9).
  - PCSK9 binds to the LDL receptors on the surface of hepatocytes to promote their degradation within the liver.
  - By inhibiting the binding of PCSK9 to LDL receptors, the number of LDL receptors available to clear LDL increases, thereby lowering LDL-C levels

- Cost is a key barrier
  - Often requires prior authorizations
  - Dependent upon insurance formularies between the 2 agents
  - Difficult to keep patients on long term

ADVOCATE HEALTH

Evolocumab. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.
Alirocumab. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.

Evolocumab/Alirocumab (cont.)

- Dosing:
  - Form: subcutaneous injection
  - Evolocumab:
    - HLD: 140mg every 2 weeks OR 420mg monthly
    - HoFH: 420mg monthly OR 420mg every 2 weeks
    - HeFH: 140mg every 2 weeks OR 420mg monthly
  - Alirocumab:
    - HLD: 75-150mg every 2 weeks OR 300 mg every 4 weeks
    - HoFH OR HeFH undergoing LDL apheresis: 150mg every 2 weeks
- Most common side effect:
  - Injection site reactions (~30%)

- Clinical Impact:
  - LDL effect: ↓ 50-70%
  - TG effect: ↓ 10-20%

ADVOCATE HEALTH

Evolocumab. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.
Alirocumab. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.

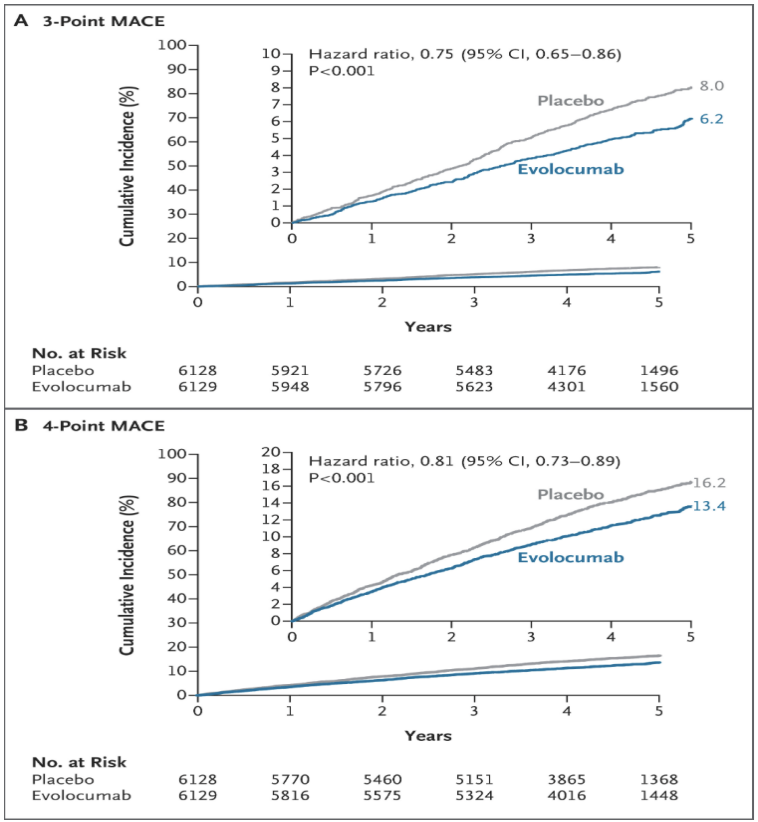
Evolocumab: VESALIUS-CV Trial

- The effect of PCSK9i on the risk of MACE among patients without a previous myocardial infarction or stroke is unknown.
- Patients were randomly assigned in a 1:1 ratio to receive evolocumab at a dose of 140 mg every 2 weeks or placebo.
- The two primary end points were a composite of death from coronary heart disease, myocardial infarction, or ischemic stroke (3-point MACE) and a composite of 3-point MACE or ischemia-driven arterial revascularization (4-point MACE).

ADVOCATE HEALTH

Bohula EA, Marston NA, Bhatia AK, et al. Evolocumab in Patients without a Previous Myocardial Infarction or Stroke. N Engl J Med. 2026;394(2):117-127. doi:10.1056/NEJMoa2514428

VESALIUS-CV Trial - Endpoints



- 3-point MACE: 6.2% with evolocumab vs 8.0% with placebo → 25% risk reduction.
- 4-point MACE: 13.4% with evolocumab vs 16.2% with placebo → 19% risk reduction

ADVOCATE HEALTH

Bohula EA, Marston NA, Bhatia AK, et al. Evolocumab in Patients without a Previous Myocardial Infarction or Stroke. N Engl J Med. 2026;394(2):117-127. doi:10.1056/NEJMoa2514428

Inclisiran

- Inclisiran is a small interfering RNA (siRNA) that directs catalytic breakdown of messenger RNA (mRNA) for PCSK9, thus inhibiting the expression of the PCSK9 enzyme.
  - Inhibition of PCSK9 leads to an increase in LDL-C receptor recycling and expression, which in turn increases LDL-C uptake and lowers the level of LDL-C in blood.

- Key barrier: requires significant coordination
  - Often requires prior authorizations
  - Entering treatment plans and coordinate with a pharmacy reimbursement team
  - Coordinating in-office administration

ADVOCATE HEALTH

Inclisiran. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.

Inclisiran (cont.)

- Dosing:
  - Form: subcutaneous injection
  - 284mg once, then at 3 months, then every 6 months thereafter
  - Injection must be completed in clinic or infusion center
- Most common side effects:
  - Injection site reactions (8%), arthralgia (5%), and bronchitis (4%)
- Clinical Impact:
  - LDL effect: ↓ 50%
  - TG effect: neutral

ADVOCATE HEALTH

Inclisiran. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.

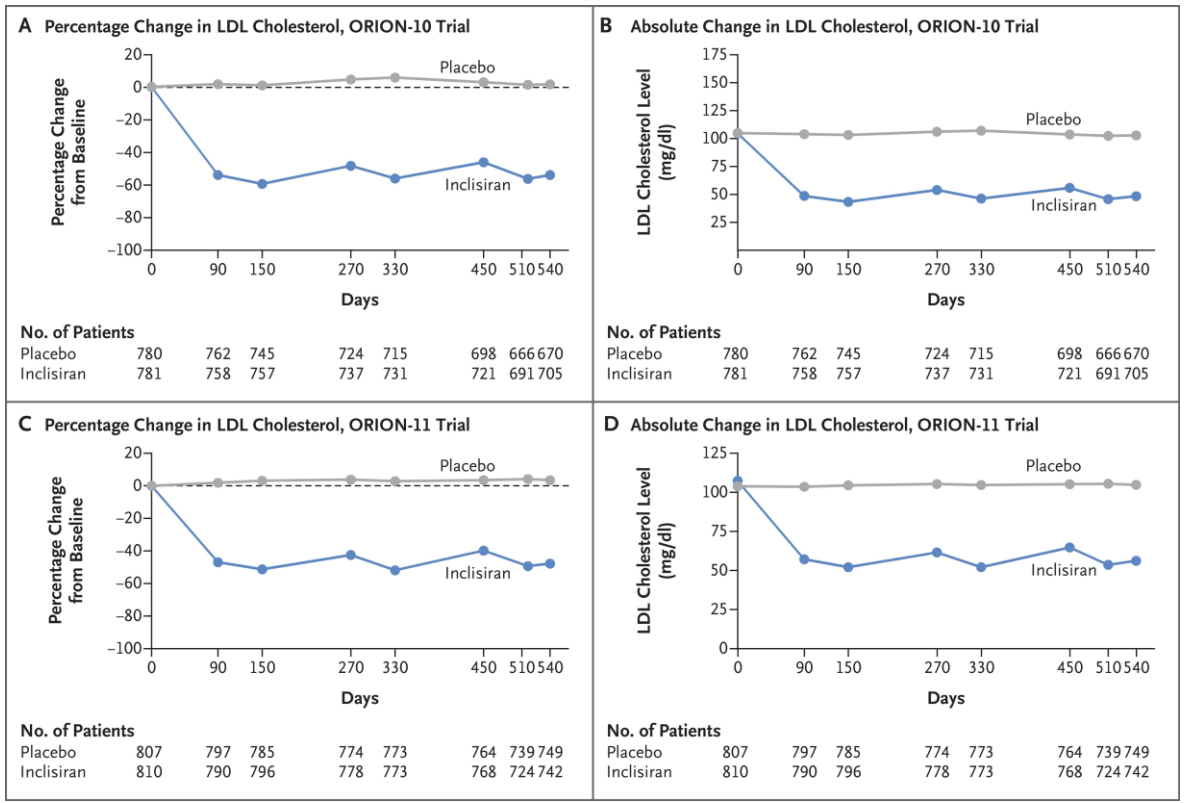
Inclisiran: ORION trials

- The ORION-10 and ORION-11 trials established inclisiran's efficacy as a non-statin lipid-lowering therapy
- These phase 3 trials enrolled 3,178 patients with ASCVD (or ASCVD risk equivalents in ORION-11) who had elevated LDL-C despite maximum tolerated statin therapy
- Randomized patients 1:1 to receive inclisiran 284 mg or placebo subcutaneously on day 1, day 90, and then every 6 months through 540 days.

ADVOCATE HEALTH

Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382(16):1507-1519. doi:10.1056/NEJMoa1912387

ORION Trials



Demonstrated sustained LDL-C reductions of approximately 50% with infrequent dosing every 6 months

(P<0.001 for all comparisons)

ADVOCATE HEALTH

Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382(16):1507-1519. doi:10.1056/NEJMoa1912387

ORION Trials - Safety

- Safety findings were reassuring, with adverse event rates similar between inclisiran and placebo groups
  - The primary safety concern was injection-site reactions, occurring in 2.6% vs. 0.9% (ORION-10) and 4.7% vs. 0.5% (ORION-11) of inclisiran vs. placebo patients
- A prespecified exploratory cardiovascular endpoint occurred less frequently with inclisiran (7.4-7.8% vs. 10.2-10.3% with placebo), though the trials were not powered for cardiovascular outcomes

ADVOCATE HEALTH

Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382(16):1507-1519. doi:10.1056/NEJMoa1912387

Inclisiran: VICTORION-Difference

- Compared inclisiran-based therapy vs optimized rosuvastatin titration in high / very-high-risk hypercholesterolemia patients (N = 1,770).

- LDL-C Goal Achievement at Day 90:
  - 84.9% with inclisiran
  - 31.0% with optimized statin therapy
  - OR 12.09; P < 0.001

- LDL-C Reduction at Day 360:
  - Inclisiran: –59.5%
  - Optimized statin therapy: –24.3%
  - Treatment difference: –35.1%; P < 0.001

ADVOCATE HEALTH

Landmesser U, Laufs U, Schatz U, et al. Inclisiran-Based Treatment Strategy in Hypercholesterolaemia: The VICTORION-Difference Trial. Eur Heart J. 2025;:ehaf685. doi:10.1093/eurheartj/ehaf685

Evinacumab

- Evinacumab-dgnb is a recombinant monoclonal antibody inhibitor of ANGPTL3. This inhibition spares the metabolic processing and clearance of VLDL upstream of LDL formation, thereby reducing LDL-C level independent of the presence of LDL receptors.
  - Angiopoietin-like protein 3 (ANGPTL3) is a protein found mainly in the liver that plays a role in lipid metabolism.

ADVOCATE HEALTH

Evinacumab. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.

Evinacumab (cont.)

- Dosing
  - Form: IV infusion
  - 15mg/kg every 4 weeks
- Most common side effects:
  - Nasopharyngitis (16%), infusion reactions (7%), influenza-like illness (7%), dizziness (6%), rhinorrhea (5%), and nausea (5%)
- Clinical Impact:
  - LDL effect: ↓ ~50%
  - TG effect: ↓ 50-60%

ADVOCATE HEALTH

Evinacumab. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.

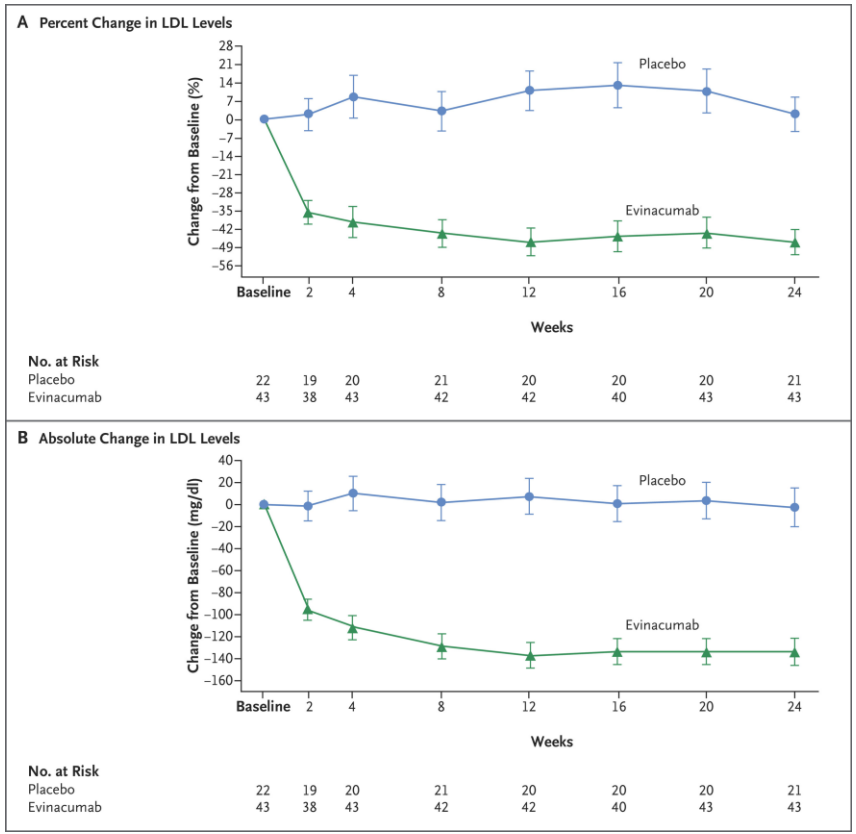
Evinacumab: ELIPSE Trial

- Randomized 65 patients with HoFH 2:1 to receive evinacumab 15 mg/kg IV every 4 weeks or placebo
- Despite background therapy including statins (77%), ezetimibe (75%), PCSK9 inhibitors (77%), lomitapide (25%), and lipoprotein apheresis (34%), baseline LDL-C remained elevated at 255 mg/dL
- The primary outcome was the percent change in the calculated LDL cholesterol level from baseline to week 24 during the double-blind treatment period

ADVOCATE HEALTH

Raal FJ, Rosenson RS, Reeskamp LF, et al. Evinacumab in homozygous familial hypercholesterolemia. *N Engl J Med*. 2020;383(8):711-720. doi:10.1056/NEJMoa2004215

ELIPSE TRIAL: Endpoint



Evinacumab reduced LDL-C by 49% at week 24 ($p<0.0001$)

ADVOCATE HEALTH

Raal FJ, Rosenson RS, Reeskamp LF, et al. Evinacumab in homozygous familial hypercholesterolemia. *N Engl J Med*. 2020;383(8):711-720. doi:10.1056/NEJMoa2004215

Lomitapide

- Lomitapide inhibits MTP, blocking the synthesis of chylomicrons and VLDL. This ultimately leads to LDL-C reduction
  - Microsomal triglyceride transfer protein (MTP) is a protein located within the lumen of endoplasmic reticulum that plays a key role in the assembly of chylomicrons and very low density lipoproteins (VLDLs) by transferring triglycerides to apolipoprotein-B

ADVOCATE HEALTH

Lomitapide. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.

Lomitapide (cont.)

- Dosing
  - Form: capsule
  - 5 mg daily; increase to 10 mg after 2 weeks, titrate every 4 weeks to max 60 mg/day.
  - Requires strict adherence to low-fat diet and slow titration to avoid GI side effects
  - Requires daily dosing of certain vitamins
    - Vitamin E, linoleic acid, alpha-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid
- Most common side effects:
  - Black box warning: may cause elevations in LFTs (adjust dose if LFT > 3x ULN)
  - Diarrhea (79%), nausea (65%), dyspepsia (38%), vomiting (34%), abdominal pain (34%), abdominal discomfort (21%), abdominal distension (21%), constipation (21%), flatulence (21%), GERD (10%), defecation urgency (10%)
- Clinical Impact:
  - LDL effect: ↓ 40-50%
  - TG effect: ↓ 40-60%

ADVOCATE HEALTH

Lomitapide. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.

Lomitapide Trial

- Design: 78-week open-label, dose-titration Phase III trial
- Population: 29 adults with HoFH
- Outcomes:
  - ~50% LDL-C reduction at week 26
  - Sustained LDL-C reduction during long-term extension (up to 126 weeks)
  - Majority of patients achieving LDL-C <100 mg/dL at least once during extended follow-up (74%)
- Established lomitapide's efficacy and led to FDA approval

ADVOCATE HEALTH

Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet. 2013;381(9860):40-46. doi:10.1016/S0140-6736(12)61731-0

Assessment Question #2

Which non-statin lipid agent inhibits ANGPTL3, which plays a role in lipid metabolism?

a) Inclisiran
b) Evinacumab
c) Evolocumab
d) Lomitapide

Summary

Drug/Class	Mechanism	LDL Effect	HDL Effect	TG Effect
Ezetimibe	Inhibits NPC1L1 → ↓ cholesterol absorption	↓ 15–25%	↑ 1–3%	↓ 5–10%
PCSK9 inhibitors (alirocumab, evolocumab)	↑ LDL receptor recycling → ↑ LDL clearance	↓ 50–70%	↑ 5–10%	↓ 10–20%
Inclisiran (siRNA)	Silences PCSK9 production	↓ 50%	Neutral	Neutral
Evinacumab	Inhibitor of ANGPTL3	↓ 49% (incremental reduction)	↓ 10-30%	↓ 50-60%
Lomitapide	Inhibitor of MTP	↓ 40% (incremental reduction)	5-20%	40-60%
Bempedoic acid	Inhibits ATP-citrate lyase (cholesterol synthesis)	↓ 15–20% (30% w/ ezetimibe)	↑ 2–3%	↓ 5–10%
Bile acid sequestrants (cholestyramine, colesevelam, colestipol)	Bind bile acids → ↑ cholesterol excretion → ↑ LDL receptor	↓ 15–25%	↑ 3–5%	↑ 10-20%
Fibrates (fenofibrate, gemfibrozil)	PPAR-α agonist → ↑ LPL activity, ↓ VLDL	↓ 5–20% (variable)	↑ 10–20%	↓ 30–50%
Omega-3 fatty acids (EPA/DHA)	↓ hepatic TG synthesis, ↑ clearance	Neutral or ↑ (with DHA), Neutral or ↓ (with EPA)	↑ 5–10%	↓ 20–50%
Niacin	↓ hepatic VLDL synthesis, ↓ adipose lipolysis	↓ 10–20%	↑ 15–35%	↓ 20–30%

Pipeline Drugs

- Lipoprotein(a) therapies: pelacarsen, olpasiran
- PCSK9 inhibitors: lerodalcibep, enlicitide decanoate (oral), CRISPR base-editing therapy
- ApoC-III inhibitors: olezarsen, plozasiran
- ANGPTL3 inhibitors: zodisaran, solbinsiran
- CETP inhibitors: obicetrapib
- FGF21 Analogs: pegozafermin
- Several others in phase 1 trials

Non-statin use: Appropriateness in Secondary Prevention

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Ezetimibe vs PCSK9i

- Ezetimibe may be preferred as the initial nonstatin agent in those requiring <25% additional LDL reduction, while a PCSK9 mAb may be preferred in those requiring >25% additional LDL reduction.
- The simultaneous addition of two agents may be considered in patients requiring greater LDL reduction than likely achievable with one agent alone

ADVOCATE HEALTH

Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 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. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

PCSK9i vs Inclisiran

- Consider replacing PCSK9 mAb with inclisiran in those with PCSK9 mAb adherence or tolerability issues.
- PCSK9 mAbs (alirocumab, evolocumab) are currently the preferred PCSK9 inhibitors over inclisiran due to available safety and CV outcomes data.
- If inclisiran is used, it should replace the PCSK9 mAb as there is no evidence or mechanistic plausibility for use together.
  - Consider referral to lipid specialist for use

ADVOCATE HEALTH

Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 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. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

Assessment Question #3

In the ORION Trials, Inclisiran demonstrated LDL-lowering by approximately what percentage?

a) 30%
b) 40%
c) 50%
d) 70%

Non-statin use: Primary Prevention

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Place in Therapy

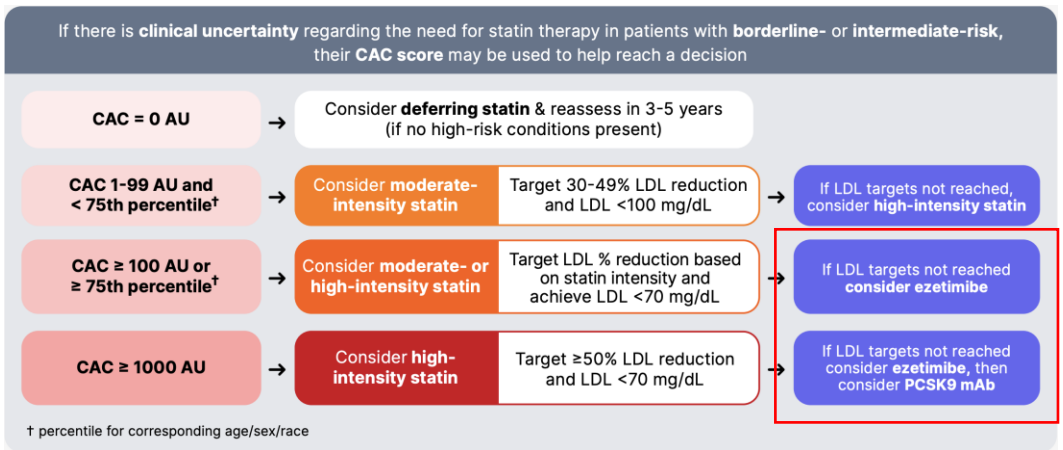
- PCSK9 mAbs, inclisiran, and bempedoic acid currently do not have an established place in therapy for primary prevention in patients with diabetes without either ASCVD or baseline LDL ≥190 mg/dL

ADVOCATE HEALTH

Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 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. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

Utilizing CAC Score

- If there is clinical uncertainty regarding the need for additional nonstatin therapy in patients with borderline or intermediate ASCVD risk, their Coronary Artery Calcium (CAC) score may be used to help reach a decision



ADVOCATE HEALTH

Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 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. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

Case Study

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J.R., a 68-year-old woman presenting to clinic for an initial visit for lipid management. She has a longstanding history of hypercholesterolemia with baseline LDL-C values consistently ≥190 mg/dL prior to treatment.

PMH:

- STEMI in 2012 (s/p PCI with drug-eluting stents to the LAD and RCA)
- CKD Stage 3a
- HTN

Current HLD Medications:

- Rosuvastatin 5 mg daily (max tolerated dose)
  - History of intolerance to multiple other statins, including simvastatin and atorvastatin

Recent Labs:

- LDL: 112 mg/dL
- HDL: 48 mg/dL
- TC: 205 mg/dL
- TG: 298 mg/dL

Assessment

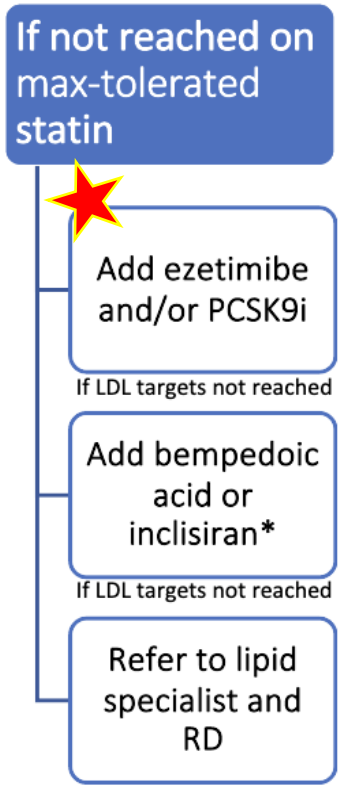
- J.R. is considered at very high risk of recurrent ASCVD events according to the 2022 ACC ECDP on LDL-C Lowering
- Therapy goals would be a ≥ 50% reduction in LDL-C and an absolute LDL-C of ≤ 55 mg/dL, which has not currently been achieved.
- Requires an additional 49% reduction from current LDL level to achieve these goals.

ADVOCATE HEALTH

Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 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. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

Therapy Selection

Drug/Class	LDL Effect	HDL Effect	TG Effect
Ezetimibe	↓ 15–25%	↑ 1–3%	↓ 5–10%
PCSK9 inhibitors (alirocumab, evolocumab)	↓ 50–70%	↑ 5–10%	↓ 10–20%
Inclisiran (siRNA)	↓ 50%	Neutral	Neutral
Bempedoic acid	↓ 15–20% (30% w/ ezetimibe)	↑ 2–3%	↓ 5–10%



PCSK9 mAb preferred in those requiring >25% additional LDL reduction

ADVOCATE HEALTH

Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 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. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

Therapy Initiation and Monitoring

- Plan: Initiate evolocumab 140 mg every 2 weeks
- Monitoring for evolocumab primarily involves serial lipid panels and clinical assessment for adverse effects
  - Lipid levels checked at 4-12 weeks after initiation or dose change, then every 3-6 months once stable
- No routine hepatic or renal dose adjustment is necessary based on mild-to-moderate hepatic impairment or renal impairment
- No clinically meaningful drug-drug interactions have been identified with evolocumab

ADVOCATE HEALTH

Evolocumab. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. http://online.lexi.com. Accessed January 28th, 2026.

Summary/Conclusion

Key Guidelines & Risk Stratification

- ACC 2022 pathway emphasizes % LDL-C reduction as strongest predictor of benefit.
- Targeting ≥ 50% LDL reduction

Therapy Selection (Place in Therapy)

- Ezetimibe: First add-on if <25% further LDL reduction needed.
- PCSK9 inhibitors (evolocumab, alirocumab): Preferred when >25% additional LDL reduction needed.
- Inclisiran: Consider when PCSK9 mAbs are limited by adherence/tolerability (not combined).
- Bempedoic acid: Option for statin-intolerant patients; ~20–30% LDL reduction.
- Evinacumab / Lomitapide: Reserved for HoFH; specialist-managed.
- Omega-3 fatty acids (Icosapent ethyl): Strong outcome data (REDUCE-IT).
- Fibrates, BAS, niacin: TG-lowering or niche roles; limited ASCVD outcomes benefit.

Clinical Trial Highlights

- CLEAR Outcomes: Bempedoic acid ↓ MACE-4 by 13% in statin-intolerant pts.
- REDUCE-IT: Icosapent ethyl ↓ primary CV events by 25% (NNT 21).
- ORION Trials: Inclisiran ~50% sustained LDL-C lowering with twice-yearly dosing.
- ELIPSE: Evinacumab ↓ LDL-C by 49% in HoFH despite maximal therapy.
- VESALIUS-CV: Evolocumab showed 25% reduction in MACE-3 and 19% reduction in MACE-4

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Questions?

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