Making Sense of Non-Statin Lipid-Lowering Therapies: The When and Why to Use Them

Ramzi Dudum, MD, MPH
Assistant Professor
Co-Director, Cardiac Rehabilitation and Wellness
University of California
San Francisco, CA

CONTINUING EDUCATION COMPANY

1

Disclosure

Advisory Board: Novartis

Research Grant: DalCor

Stockholder: Centene; Walmart

CONTINUING EDUCATION COMPANY

2

Learning Objectives

1. Describe commonly used lipid-lowering therapies
2. Describe drug-specific considerations
3. Consider special situations for lipid lowering therapies

Lipid Lowering Agents (LDL-C)

Statins

Low (<30%)	Medium (30-49%)	High (50+%)
Fluvastatin <40mg Lovastatin <20mg	Atorvastatin <20mg Rosuvastatin <10mg	Atorvastatin 40-80mg Rosuvastatin 20-40mg
Pravastatin <20mg Simvastatin <10mg	Fluvastatin 80mg Lovastatin 40mg-80mg Pitavastatin 1-4mg Pravastatin 40-80mg Simvastatin 20-40mg	

Adapted from Blumenthal RS, et al. https://doi.org/10.1161/CIR.0000000000001423

Lipid Lowering Agents (LDL-C)

Non-Statins

Ezetimibe 10mg	Alirocumab 75-150mg Evolocumab 140mg Inclisiran 284mg
Bempedoic Acid 180mg	Cholestyramine 8-16g Colesevelam 3.75mg Colestipol 2-16g

Adapted from Blumenthal RS, et al. https://doi.org/10.1161/CIR.0000000000001423

5

Estimated LDL-C Reduction

Rosuvastatin 5-40mg

Atorvastatin 10-80mg

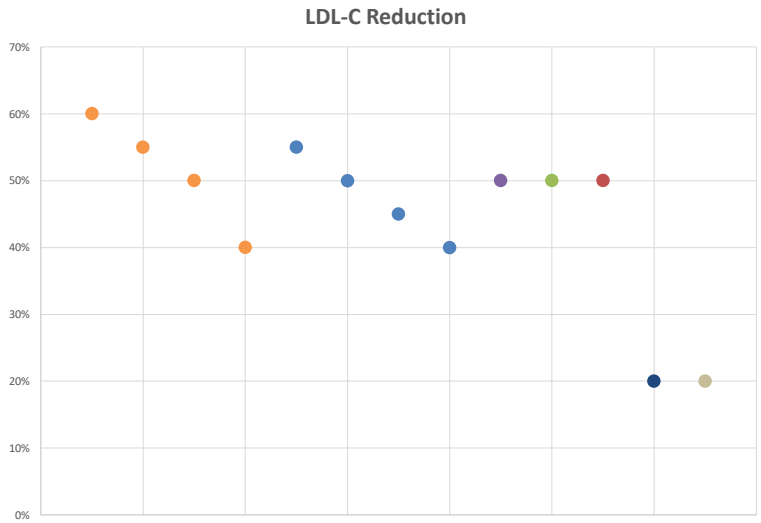
Evolocumab

Alirocumab

Inclisiran

Ezetimibe

Bempedoic Acid



Adapted from Blumenthal RS, et al. https://doi.org/10.1161/CIR.0000000000001423
Adapted from https://www.uptodate.com/contents/search?search=statin%20comparison%20chart

6

Ezetimibe

- Evidence
  - Cardiovascular outcomes trials
    - IMRPOVE-IT

Cannon CP, et al. DOI: 10.1056/NEJMoa1410489

7

IMPROVE-IT (2015)

- Population: >18,000 individuals, 50+ years old with recent ACS
- Intervention: Ezetimibe 10mg (+Simvastatin 40mg)
- Comparison: Simvastatin 40mg
- Outcome: Composite MACE
  - **HR 0.94 (0.89-0.99, P=0.016)**

Key Points

- Trial starting LDL-C
  - 94mg/dL
- Median FU LDL-C
  - 54mg/dL
- NNT: 50

Cannon CP, et al. DOI: 10.1056/NEJMoa1410489

8

Specific Considerations for Ezetimibe

- Statin intolerance and need for modest LDL-C reduction — LDL-C start-goal gap is large, may not be enough
- Generally, well-tolerated with low rates of myalgias
- Generic drug
- CKD: OK, Hepatic impairment: may increase concentration

Ezetimibe FDA Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021445s042lbl.pdf

9

PCSK9 Inhibitors

- Evidence
  - Cardiovascular outcomes trials
    - FOURIER
    - ODYSSEY
    - VESALIUS

Sabatine MS, et al. DOI: 10.1056/NEJMoa1615664
Schwartz GG., et al. DOI: 10.1056/NEJMoa1801174
Bohula EA, et al. DOI: 10.1056/NEJMoa2514428

10

Fourier (2017)

- Population: >27,000 individuals, age 40-85 with clinical ASCVD, baseline LDL-C >70mg/dL
- Intervention: evolocumab (140mg q2w or 420mg qMonth)
- Comparison: Placebo
- Outcome: Composite MACE
  - **HR 0.85 (0.79 to 0.92, p<0.001)**

Key Points
- Trial starting LDL-C
  - 92mg/dL
- Median FU LDL-C
  - 30mg/dL
- NNT: 67

Sabatine MS, et al. DOI: 10.1056/NEJMoa1615664

11

Odyssey (2018)

- Population: ~19,000 individuals, >40yo with ACS (w/in 1-12m) and baseline LDL-C >70mg/dL
- Intervention: alirocumab 75mg q2w
- Comparison: Placebo
- Outcome: Composite MACE
  - **HR 0.85 (0.78 to 0.93, p<0.001)**

Key Points
- Trial starting LDL-C
  - 92mg/dL
- Median FU LDL-C
  - 48mg/dL
- NNT: 63

Schwartz GG, et al. DOI: 10.1056/NEJMoa1801174

12

Vesalius (2026)

- Population:
  - Primary prevention, i.e. without MI/CVA and ≥ criteria from "coronary artery disease, atherosclerotic cerebrovascular disease, peripheral artery disease, or high-risk diabetes"
    - CAD: CAC≥100, PCI, mvCABG ≥5 years prior
    - CVA: TIA with ≥50% lesion or ≥70% lesion
    - PAD: Abnormal ABI or ≥50% stenosis
    - DM: Long-standing DM or microvascular dz or insulin

Bohula EA, et al. DOI: 10.1056/NEJMoa2514428

13

Vesalius (2026)

- Population: ~12,000 individuals, ≥ 50yo (M) or ≥55yo (W) and <80yo, LDL-C >90mg/dL
- Intervention: evolocumab 140mg q2w
- Comparison: Placebo
- Outcome: 3-point MACE and 4-point MACE
  - **HR 0.75 (0.65 to 0.86, p<0.001)**

Key Points
- Trial starting LDL-C
  - 122mg/dL
- Median FU LDL-C*
  - 45mg/dL
- NNT: 36-56

*In ~2000 from Lipid substudy

Bohula EA, et al. DOI: 10.1056/NEJMoa2514428

14

Specific Considerations for PCSK9i's

- Statin intolerance and need for significant LDL-C reduction
- Not-generic, often requires co-pay and prior authorization
- Generally, higher adherence and cumulative LDL-C reduction

Sabatine MS, et al. DOI: 10.1056/NEJMoa1615664
Schwartz GG, et al. DOI: 10.1056/NEJMoa1801174
Bohula EA, et al. DOI: 10.1056/NEJMoa2514428

15

Trial Comparison

	FOURIER	ODYSSEY	VESALIUS
Populations	Clinical ASCVD	ACS >1 month and <12 month	Very high-risk primary prevention
HR	0.85 (0.79 to 0.92, p<0.001)	0.85 (0.78 to 0.93, p<0.001)	0.75 (0.65 to 0.86, p<0.001)
NNT	67	~40-63	36-56

Sabatine MS, et al. DOI: 10.1056/NEJMoa1615664
Schwartz GG, et al. DOI: 10.1056/NEJMoa1801174
Bohula EA, et al. DOI: 10.1056/NEJMoa2514428

16

Lp(a) Strata

- Post-Hoc Analysis of ODYSSEY Outcomes

	Low LDL-C (<70mg/dL)	High LDL-C (≥70mg/dL)
Lp(a) ≤ 13.7mg/dL	↔	↓
Lp(a) > 13.7mg/dL	↓	↓

Takeaways:
1) If LDL-C not at goal, PCSK9i helps
2) If LDL-C <70mg, Lp(a) can inform aggressive reduction

Schwartz GG, et al. doi: 10.1016/j.jacc.2021.04.102

17

ARS Question 1

What Is Currently FDA Approved for Treatment of Hypercholesterolemia as an Adjunct to Diet?

A. Statin therapy
B. Ezetimibe therapy
C. PCSK9 inhibitor therapy
D. A & B
E. All of the above

PCSK9 siRNA-Inclisiran

- Evidence
  - ORION-10
  - ORION-11

19

ORION-10 & 11 (2020)

- Population: 3100 patients with either ASCVD and LDL-C ≥70mg/dL or ASCVD equivalent and LDL-C ≥100mg/dL
- Intervention: inclisiran 284mg
- Comparison: Placebo
- Outcome: % change in LDL-C
  - -49.9% and -52.3% in the two trials

Ray KK, et al. DOI: 10.1056/NEJMoa1912387

20

Ongoing CVOT Outcome Trials

- ORION-4: ≥40M or ≥55F and history of ASCVD randomized to inclisiran and followed up for MACE
- VICTORION-2 PREVENT: ≥40yo w/ established ASCVD randomized to inclisiran and followed up for MACE

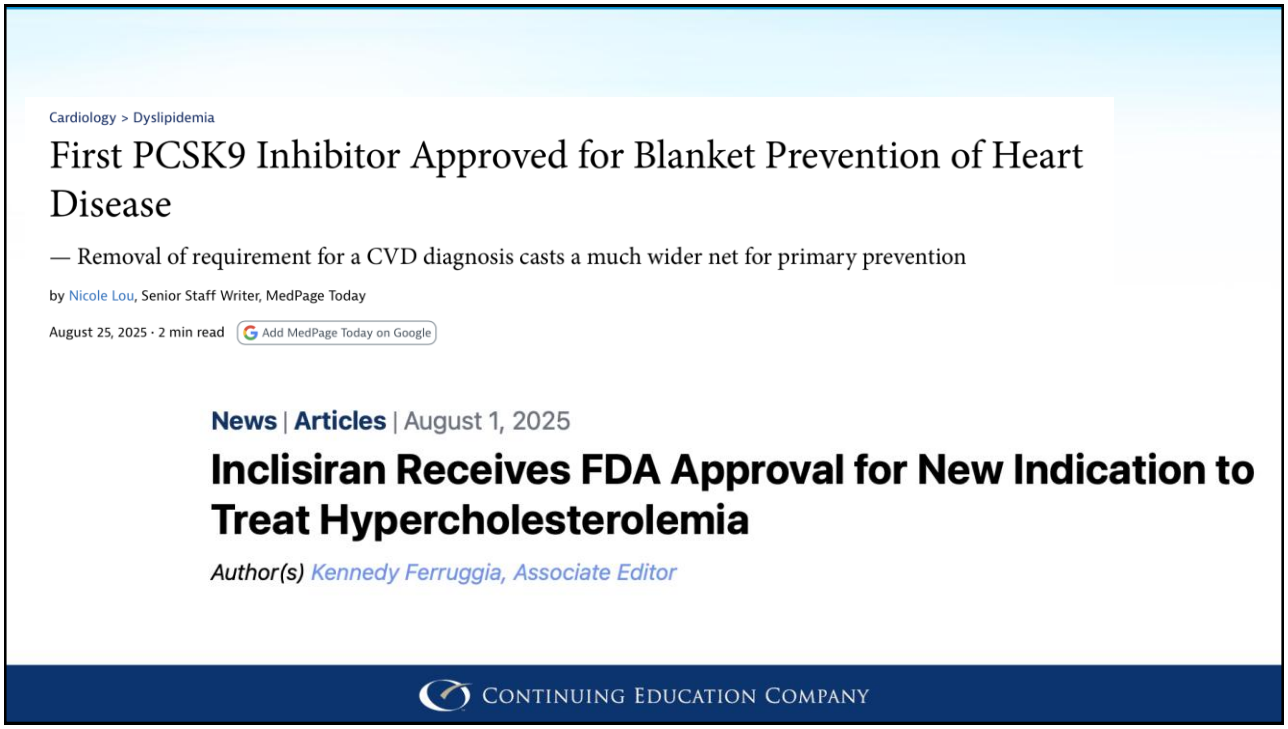
Clinical Trials, https://clinicaltrials.gov/study/NCT03705234
Clinical Trials, https://clinicaltrials.gov/study/NCT05030428

21

Specific Considerations - Inclisiran

- Unable to tolerate other PCSK9i
- Preference for less frequent dosing
  - Dose at 1m, 3m, 6m ongoing
- Projected to have highest cumulative LDL-C reduction due to improved adherence

22



Cardiology > Dyslipidemia

First PCSK9 Inhibitor Approved for Blanket Prevention of Heart Disease

— Removal of requirement for a CVD diagnosis casts a much wider net for primary prevention

by Nicole Lou, Senior Staff Writer, MedPage Today

August 25, 2025 · 2 min read Add MedPage Today on Google

News | Articles | August 1, 2025

Inclisiran Receives FDA Approval for New Indication to Treat Hypercholesterolemia

Author(s) Kennedy Ferruggia, Associate Editor

CONTINUING EDUCATION COMPANY

23

Bempedoic Acid

- Evidence
  - CLEAR Harmony
  - CLEAR Wisdom
  - CLEAR Serenity and Tranquility
  - CLEAR Outcomes

24

Trial Comparison

CLEAR HARMONY	CLEAR WISDOM	CLEAR SERENITY	CLEAR TRANQUILITY	CLEAR OUTCOMES
Patients on background statin therapy	Patients on background statin therapy	Statin intolerant patients	Statin intolerant patients on ezetimibe therapy	Statin intolerant patients

Goldberg AC, et al. doi:10.1001/jama.2019.16585
Laufs U, et al. https://doi.org/10.1161/JAHA.118.011662
Banach M, et al. doi:10.1001/jamacardio.2020.2314
Nissen SE, et al. DOI: 10.1056/NEJMoa2215024

25

Pooled CLEAR Data

- Population: CLEAR- WISDOM, SERENITY, HARMONY and TRANQUILITY
  - Patients with ASCVD +/- HeFH
- ~3000 patients on max tolerated statin
  - 97% with ASCVD, 3.7% with HeFH
  - Starting LDL-C was ~108mg/dL
- ~600 patients with statin intolerance
  - Starting LDL-C was ~144mg/dL

Banach M, et al. doi:10.1001/jamacardio.2020.2314

26

Pooled CLEAR Data

- Intervention: Bempedoic Acid
- Comparison: Placebo
- Outcome:
  Compared to Placebo, LDL-C % change:
  - **-17.8%** in those on max statin therapy
  - **-24.5%** in statin intolerant patients

Banach M, et al. doi:10.1001/jamacardio.2020.2314

27

CLEAR Outcomes (2023)

- Population: ≥ 18yo, ~14,000 1º and 2º prevention, statin intolerant
- Intervention: Bempedoic Acid
- Comparison: Placebo
- Outcome: MACE
  - **HR 0.87 (0.79 to 0.96, p=0.004)**

Key Points
- Trial starting LDL-C
  - 139mg/dL
- Mean FU LDL-C
  - 110mg/dL
- NNT: 63

Nissen SE, et al. DOI: 10.1056/NEJMoa2215024

28

Special Considerations

- Great tool for statin intolerant patients, with robust evidence
  - Modest reduction alone (~20%), improved reduction with ezetimibe combo (~40%)
- Monitor for hyperuricemia and gout; avoid in patients with history of tendon pathology

FDA Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/211616s026lbl.pdf

29

ARS Question 2

A 68-year-old patient without ASCVD has a 10-year PREVENT-ASCVD risk of 11.3% and CAC score of 432AU who has a starting LDL-C of 138mg/dL and has discontinued atorvastatin and pravastatin due to myalgias, which resolved with cessation.

Which Drug Would You Select?

A. Alirocumab
B. Ezetimibe
C. Bempedoic acid
D. Hydrophilic statin

Lipoprotein Goals for ASCVD Risk Reduction

Patient population	LDL-C <100 mg/dL (2.6 mmol/L) Non-HDL-C <130 mg/dL (3.4 mmol/L)	LDL-C <70 mg/dL (1.8 mmol/L) Non-HDL-C <100 mg/dL (2.6 mmol/L)	LDL-C <55 mg/dL (1.4 mmol/L) Non-HDL-C <85 mg/dL (2.2 mmol/L)
Primary prevention	PREVENT-ASCVD < 10% • If TG ≥ 150 mg/dL to 499 mg/dL, apoB goal: <90 mg/dL	PREVENT-ASCVD ≥ 10% • If TG ≥ 150 mg/dL to 499 mg/dL, apoB goal: <70 mg/dL	N/A
Severe hypercholesterolemia	**Without** FH, ASCVD risk factors, and subclinical atherosclerosis	**With** FH, ASCVD risk factors, and subclinical atherosclerosis	Severe hypercholesterolemia or HeFH with clinical ASCVD
Diabetes	**Without** ASCVD risk factors or diabetes-specific risk modifiers • apoB goal: <90 mg/dL	**Without** ASCVD risk factors or diabetes-specific risk modifiers • apoB goal: <70 mg/dL	N/A
Subclinical atherosclerosis	CAC = 1-99 AU and <75th percentile for age, sex, and race	• CAC ≥ 100 to 299 AU or ≥75th percentile for age, sex, and race • CAC ≥ 300 to 999 AU – Optional goal: LDL-C <55 mg/dL, non-HDL-C <85 mg/dL, and consider apoB goal <55 mg/dL	CAC ≥ 1000 AU
Hypertriglyceridemia	<50 y old with no additional risk enhancers	• With clinical ASCVD not at very high risk – apoB goal: <70 mg/dL • Age 40-75 y with ≥1 ASCVD risk factor – apoB goal: <70 mg/dL	• With clinical ASCVD at very high risk – apoB goal: <55 mg/dL
Clinical ASCVD	N/A	Not at very high risk • Optional goal: LDL-C <55 mg/dL, non-HDL-C <85 mg/dL, and consider apoB goal <55 mg/dL	• At very high risk – apoB goal: <55 mg/dL • With CKD

American Heart Association.

Abbreviations: ApoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; AU, Agatston units; CAC, coronary artery calcium; CKD, chronic kidney disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; and TG, triglycerides.

Blumenthal, R.S., Morris, P.B., et al. 2026 ACC/AHA Guideline on the Management of Dyslipidemia. *Circulation*.

31

ARS Question 3

All of the Following Drugs Have Outcome Data, *Except:*

A. Evolocumab
B. Inclisiran
C. Ezetimibe
D. A & C
E. All of the above

CONTINUING EDUCATION COMPANY

32

Triglyceride Lowering Agents

Fenofibrate and fibrate derivatives	Omega-3 Fatty Acids -Icosapent Ethyl 2g BID	Olezarsen 80mg monthly

Adapted from Blumenthal RS, et al. https://doi.org/10.1161/CIR.0000000000001423

33

REDUCE-IT (2018)

- Population: 8200 individuals, ≥45yo w/ ASCVD or ≥50 w/ risk factors; TGL 150-499mg/dL and LDL 41-100mg/dL
- Intervention: icosapent ethyl 2g BID
- Comparison: Placebo
- Outcome: MACE
  - **HR 0.87 (0.79 to 0.96, p=0.004)**
  - **NNT of**

Bhatt DL, et al. DOI: 10.1056/NEJMoa1812792

34

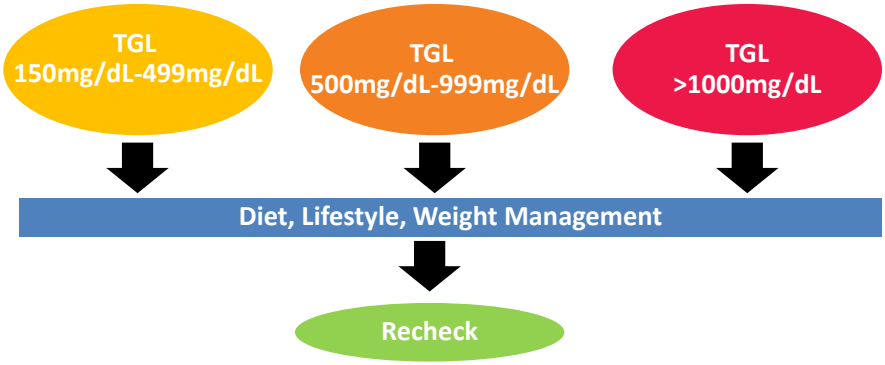
Olezarsen-APOC-III Inhibitor

- Population: ≥18yo with TGL ≥500mg/dL (2x)
- Intervention: 1:1:1 (Olezarsen 50mg and 80mg) on background lipid therapy
- Comparison: Placebo
- Outcome: % change in TGL
  - Change of -63% to 73% in Olezarsen groups vs. (0 to -14% in Placebo)
  - NNT to avoid pancreatitis was 20

Marston NA, et al. *NEJM* January 29, 2026;394:429-441.

35

By TGL Level



*Based on PREVENT and risk discussion

Adapted from Blumenthal RS, et al. https://doi.org/10.1161/CIR.0000000000001423

36

GLP1-RA

- We will cover two most potent GLP1-RA for weight loss:
  - Tirzepatide
  - Semaglutide

37

STEP-1 (2021)

Key Inclusion	• At least 1 unsuccessful weight loss attempt • BMI ≥ 30kg/m^2 or BMI ≥ 27kg/m^2 *AND* obesity related complication
Key Exclusion	• Diabetes Mellitus, Hx of Pancreatitis
Randomization	• 2: 1 to semaglutide vs. placebo
Key Outcomes	• Co-Primary Endpoints: Percent weight Δ from baseline and weight reduction ≥ 5%
Results	• Mean Age: 46, 74% Female, 75% White • Mean BMI at randomization: 37.9kg/m^2 • Compared to placebo **(-14.9% vs. -2.4%)** • At least 86% of participants reached ≥ 5% weight reduction (compared to 32% for placebo)

Wilding JPH, et al. DOI: 10.1056/NEJMoa2032183

38

SURMOUNT-1 (2022)

Key Inclusion	• BMI ≥ 30kg/m^2 • BMI ≥ 27kg/m^2 *AND* an obesity related complication
Key Exclusion	• Diabetes Mellitus
Randomization	• 1: 1: 1: 1 Tirzepatide doses vs. Placebo
Key Outcomes	• Co-Primary Endpoints: Percent weight Δ from baseline and weight reduction ≥ 5%
Results	• Mean Age: 45, 68% Female, 71% White • Mean BMI at randomization: 38kg/m^2 • Significant weight loss (-15% to -20.9%) compared to placebo (-3.1%) • At least **85%** of participants reached ≥ 5% weight reduction (compared to 35% for placebo)

Jastreboff AM, et al. DOI: 10.1056/NEJMoa2206038

39

TGL Lowering in STEP-1 and SURMOUNT-1

	STEP-1, Semaglutide	SURMOUNT-1, Tirzepatide
Abs. Change from Baseline	Estimated decrease ~20mg/dL	Estimated decrease 26mg/dL
% Change from Baseline	-16%*	-20.3%

*Ratio to baseline comparing semaglutide to placebo

Wilding JPH, et al. DOI: 10.1056/NEJMoa2032183
Jastreboff AM, et al. DOI: 10.1056/NEJMoa2206038

40

GLP1-RA Take Homes

- If metabolic milieu predominates, treat the metabolic milieu
- Majority of GLP1-RA studies had a large proportion of CV disease at baseline (definition included CKD)
- Improvements in A1C seen, and either reduction in CV events or non-inferiority
- Weight loss seen independent of baseline diabetes
- Obesity trials had a higher baseline BMI

41

GLP1-RA Take Homes

- If indication is obesity (and no DM), i.e.
  - BMI ≥ 27kg/m^2 with ASCVD risk factors *or*
  - BMI ≥ 30kg/m^2
- Make sure to prescribe the obesity-specific medication
- Coverage landscape is ever-evolving, often requires PA

42

Considerations in Pregnancy and Lactation

COR	RECOMMENDATIONS
1	Persons of childbearing age with hypercholesterolemia who are not at high risk for ASCVD and plan to become pregnant should stop statin therapy 1 to 2 months before attempting to become pregnant or as soon as pregnancy is discovered to avoid uncertain risks to the fetus.
2a	In pregnant or lactating individuals with HoFH, it is reasonable to undergo lipoprotein apheresis to lower LDL-C and reduce ASCVD risk.
2a	In pregnant individuals with severe fasting hypertriglyceridemia TG ≥500 mg/dL [5.7 mmol/L]), the use of fibrates (after the 1st trimester) or high-dose omega-3 ethyl esters is reasonable as an adjunct to lifestyle management to lower TG levels and reduce the risk of pancreatitis.

American Heart Association.

Abbreviations: ASCVD indicates atherosclerotic cardiovascular disease; HoFH, homozygous familial hypercholesterolemia; and TG, triglycerides.

Blumenthal, R.S., Morris, P.B., et al. 2026 ACC/AHA Guideline on the Management of Dyslipidemia. *Circulation*.

43

Considerations in Pregnancy and Lactation (Continued)

COR	RECOMMENDATIONS
2a	In pregnant or lactating individuals with hypercholesterolemia but without hypertriglyceridemia, the use of bile acid sequestrants is reasonable to lower LDL-C.
2b	In pregnant individuals with FH or a history of clinical ASCVD, it may be reasonable to continue statin therapy to lower LDL-C and ASCVD risk following individualized benefit-risk discussion.

American Heart Association.

Abbreviations: ASCVD indicates atherosclerotic cardiovascular disease; and LDL-C, low-density lipoprotein cholesterol.

Blumenthal, R.S., Morris, P.B., et al. 2026 ACC/AHA Guideline on the Management of Dyslipidemia. *Circulation*.

44

Female-Specific Considerations

- Take a history for APO in every female patient
- Incorporate reproductive and family-planning goals into decision
- If on therapy, stop 1-2 months prior to attempting
- In general, if considering treatment during pregnancy/lactation, refer to lipid specialist

45

ARS Question 4

Who Should You Screen for Adverse Pregnancy Outcomes?

A. Females of childbearing age
B. Perimenopausal females
C. Post-Menopausal females
D. All of the above

CONTINUING EDUCATION COMPANY

46

ARS Question 5

What Medications Is/Are Safest in Pregnancy?

A. Simvastatin
B. Ezetimibe
C. Bile acid sequestrants
D. Alirocumab
E. Bempedoic acid

CONTINUING EDUCATION COMPANY

47

Summary

- Multiple different ways to achieve significant LDL-C reductions
  - >50% possible with high-intensity statin, PCSK9-based therapy, and non-statin orals w/ statin combo
- Patient preference may guide you (side effect profile, dosing frequency/route, cost, etc…)
- Be pragmatic with combination and affordability
- Backbone of triglyceride lowering is diet/lifestyle; address metabolic milieu if present

48