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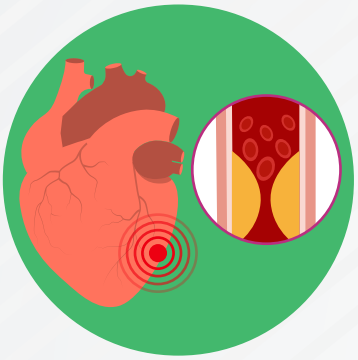
Role of Nonstatin Therapies in Lowering LDL-Cholesterol during Atherosclerotic Cardiovascular Disease Risk Management

2022 Expert Consensus Decision Pathway by the American College of Cardiology

Timeline of ASCVD management guideline development[1]



Atherosclerotic cardiovascular disease (ASCVD) continues to be a leading cause of mortality worldwide[1]

2013 — American College of Cardiology (ACC) and American Heart Association (AHA)'s "Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults"

2016 — "ACC Expert Consensus Decision Pathway on the Role of Non-statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk"

2017 — "Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk" supporting the use of PCSK9 mAbs in clinical practice

2018 — AHA/ACC/multisociety "Guideline on the Management of Blood Cholesterol" (henceforth, 2018 AHA/ACC/multisociety cholesterol guideline for ASCVD)

2018 AHA/ACC/multisociety cholesterol guideline for ASCVD[2]

- Statin therapy in the four main patient groups
- Appropriate intensity of statin therapy
- Achieving expected reductions in LDL-C
- Shared decision-making following clinician–patient discussions

Evidence-based patient management groups endorsed by the 2018 AHA/ACC/multisociety cholesterol guideline[2]

1. **Adults ≥20 years**
   - Clinical ASCVD
   - On statin therapy for secondary prevention
2. **Adults ≥20 years**
   - LDL-C ≥190 mg/dL (not due to secondary causes)
   - On statin therapy for primary prevention
3. **Adults aged 40–75 years**
   - With diabetes and without ASCVD
   - On statin therapy for primary prevention
4. **Adults aged 40–75 years**
   - Without diabetes and ASCVD
   - LDL-C 70–189 mg/dL; 10-year ASCVD risk at 7.5%
   - On statin therapy for primary prevention

Abbreviations: LDL = low density lipoprotein; mAb = monoclonal antibody; PCSK9 = proprotein convertase subtilisin/kexin type 9

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New nonstatin therapies approved by the FDA following the 2018 AHA/ACC/multisociety cholesterol guideline[2]

Bempedoic acid

- ATP-citrate lyase inhibitor
- Bempedoic acid and bempedoic acid + ezetimibe—approved for lowering LDL-C in adults with ASCVD or HeFH
- Adjunct to diet and maximally tolerated statin therapy
- Combination—useful for patients with multidrug regimen adherence issues and/or those requiring additional LDL-C lowering

Evinacumab

- Human monoclonal antibody inhibiting ANGPTL3
- Approved for lowering LDL-C in adults and paediatric patients (aged 12 years) with genetically confirmed HoFH only
- Adjunct to other LDL-C-lowering therapies

Inclisiran

- siRNA targeting PCSK9—inhibits production in the liver
- Approved for lowering LDL-C in adults with ASCVD or HeFH as adjunct to diet and maximally tolerated statin therapy
- Twice yearly subcutaneous administration—attractive aspect for patients with adherence issues

Abbreviations: ATP = adenosine triphosphate; ANGPTL3 = angiopoietin-like 3; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; siRNA = small interfering RNA

Recommendations for nonstatin use as per the 2018 AHA/ACC/multisociety cholesterol guidelines[2]

- LDL-C threshold ≥70 mg/dL for considering nonstatin therapy
- Ezetimibe recommended as the initial nonstatin
- PCSK9 monoclonal antibody (mAb) considered in high-risk patients already on maximally tolerated statins and ezetimibe
- Adding ezetimibe, PCSK9 mAb, or bile acid sequestrants (BAS) is considered in case of primary severe hypercholesterolemia (LDL-C ≥190 mg/dL)

Availability of new FDA-approved nonstatins raises questions about[2]

- Patient populations for considering nonstatin therapies
- Situations for considering nonstatin use
- Therapies and regimens for introducing nonstatins and maximizing benefit

Development of the 2022 ACC Expert Consensus[2]

- Need for expert consensus guidance regarding nonstatin usage for high-risk patients
- Real or perceived relationships with industry (RWI) avoidance policy
- Identification of higher-risk subgroups for initiating additional LDL-C lowering therapies

2022 ACC Expert Consensus Decision Pathway (ECDP)

- Current evidence regarding nonstatin therapy
- Four main patient management groups according to 2018 ACC guidelines
- Assumptions that the patient is currently/has been on statin therapy

General recommendations from 2022 ACC ECDP for clinicians[2]

- Reinforce adherence to lifestyle interventions
- Monitor response using lipid panels
- Use evidence-based statins as first-line therapy

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Pathway summary for the management of patient groups[2]

- Secondary prevention
  - Adults with clinical ASCVD
- Primary prevention
  - Adults with primary severe hypercholesterolemia (LDC-C ≥190 mg/dL [≥4.9 mmol/L])
  - Adults with diabetes
  - Adults without diabetes

Factors to consider

- Adherence to lifestyle modifications and adherence to evidence-based, guideline-recommended stain therapy
- Use of guideline-recommended statin therapy
- Risk-enhancing factors
- Control of other risk factors
- Clinician–patient decision about potential benefits, potential harms, and patients' preferences with regard to the addition of nonstatin therapies
- Percentage LDL-C reduction and absolute LDL-C or non-high-density lipoprotein cholesterol (HDL-C) level achieved
- Monitoring of response to lifestyle modifications, adherence, and therapy
- Cost of therapy
- Statin-associated side effects
- Persistent hypertriglyceridemia

Optional interventions to consider in appropriate patient groups

- Referral to a lipid specialist and registered dietitian/ nutritionist
- Ezetimibe
- BAS
- PCSK9 mAbs*
- Bempedoic acid
- Inclisiran
- LDL apheresis, if patients have familial hypercholesterolemia
- Lomitapide (only in HoFH)
- Evinacumab (only in HoFH)

Definition of major ASCVD events and high-risk conditions[2]

High-risk conditions

- Age ≥65 years
- HeFH
- 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 m^2)
- Current smoking
- Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
- History of congestive HF

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

Abbreviations: ABI = ankle-brachial index; ACS = acute coronary syndrome; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; MI = myocardial infarction; PAD = peripheral artery disease

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2022 ECDP-recommended approach for considering additional therapy in adults with clinical ASCVD[2]

Very high risk, on statin therapy for secondary prevention

Continue with statin therapy if patient achieves a ≥50% reduction in LDL-C from baseline and LDL-C <55 mg/dL with first statin treatment

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Monitor adherence to medicines, lifestyle modifications, and ongoing response to therapy

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If LDL-C ≥55 mg/dL, conduct routine clinical assessment and intervention with high-intensity statin therapy

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In case of inadequate lowering, consider adding either ezetimibe (for <25% additional LDL-C lowering) or a PCSK9 mAb (for >25% additional LDL-C lowering)

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Consider adding bempedoic acid or a second nonstatin if additional/greater LDL-C reduction is desired

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Refer to lipid specialist if LDL-C lowering is <50% despite maximally tolerated statin treatment and other adjunctive nonstatin therapy

↓

Refer to 2021 ACC ECDP guidelines for persistent hypertriglyceridemia

Not at a very high risk, on statin therapy for secondary prevention

Continue with statin therapy if ≥50% reduction in LDL-C and LDL-C is <70 mg/dL is achieved

↓

Monitor adherence to medicines, lifestyle modifications, and ongoing response to therapy

↓

If LDL-C reduction <50% and LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL, conduct routine clinical assessment and interventions (high-intensity statin and referral to lipid specialist or nutritionist)

↓

In case of inadequate lowering, consider adding ezetimibe 10 mg daily (<25% additional LDL-C lowering, recent ACS <3 months)

↓

If LDL-C lowering remains <50% or LDL-C ≥70 mg/dL, consider adding PCSK9 mAb (add/replace with ezetimibe)

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Consider two agents (statin and nonstatin) for higher LDL-C reduction

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Consider bempedoic acid for further reduction or statin and nonstatin intolerance

↓

Refer to lipid specialist for considering inclisiran prescription

Baseline LDL-C (≥190 mg/dL not due to secondary causes), on statin therapy for secondary prevention

Continue with statin therapy if ≥50% reduction in LDL-C is achieved and LDL-C is <70 mg/dL

↓

Monitor adherence to medicines, lifestyle modifications, and ongoing response to therapy

↓

If LDL-C reduction is <50% and LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL, conduct routine clinical assessment and intervention (high-intensity statins)

↓

Also consider referring to lipid specialist and nutritionist (especially if patient has documented HoFH or HeFH)

↓

In case of inadequate lowering, consider adding either ezetimibe (for <25% additional LDL-C lowering) or a PCSK9 mAb (for >25% additional LDL-C lowering)

↓

In patients with clinical ASCVD and LDL-C ≥ 190 mg/dL, consider the simultaneous addition of two agents (statin + ezetimibe, statin with/o ezetimibe, and PCSK9 mAb)

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Consider bempedoic acid for further reduction/statin and nonstatin intolerance

↓

Refer to lipid specialist for considering inclisiran prescription, and if desired LDL-C levels are not achieved

The 2022 ACC ECDP addresses the current gaps in ASCVD risk reduction necessitated by new developments since the publication of 2018 AHA/ACC/ multisociety cholesterol guidelines. It incorporates recommendations for additional therapy in four evidence-based patient management groups aimed at providing practical clinical guidance for the use of nonstatin therapies to further reduce ASCVD risk

References:

1. Barquera, S., Pedroza-Tobías, A., Medina, C., Hernández-Barrera, L., Bibbins-Domingo, K., Lozano, R., & Moran, A. E. (2015). Global Overview of the Epidemiology of Atherosclerotic Cardiovascular Disease. *Archives of Medical Research, 46(5)*, 328–338.
2. Lloyd-Jones, D. M., Morris, P. B., Ballantyne, C. M., Birtcher, K. K., Covington, A. M., DePalma, S. M., ... & Wilkins, J. T. (2022). 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. *Journal of the American College of Cardiology, 80(14),* 1–53.

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