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DEPARTMENT OF SOCIAL SERVICES
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The Role of Nonstatin Therapies in the Management of Dyslipidemia

Dyslipidemia is a chronic disease state defined by elevated levels of low-density lipoprotein (LDL-C) within the blood which can lead to the development of atherosclerotic cardiovascular disease (ASCVD), coronary artery disease (CAD), myocardial infarction (MI), and stroke. Two general categories define causation, primary dyslipidemia is a result of genetic disposition whereas secondary dyslipidemia is attributed to factors such as diet, sedentary lifestyle, or comorbid conditions. Dyslipidemia affects approximately 50% of adults in the US and it is estimated that only 35% of those are managed appropriately.[1]

Guideline and expert consensus pathways have been published over the last few decades to aid health care providers in the management of this disease. The American Heart Association (AHA) /American College of Cardiology (ACC)/ multisociety cholesterol guideline published in 2013 and 2018 define 4 patient groups (Box 1) for the management of hypercholesterolemia.[2,3]

Lifestyle modifications such as implementing a heart healthy diet, exercise, maintaining a healthy weight, and abstaining from tobacco are recommended for all 4 patient management groups. Additionally, all 4 groups should receive statin therapy. When maximally tolerated statin therapy is used and LDL goals are still not reached, these 4 patient groups can be considered for nonstatin therapy. The 2022 ACC Expert Consensus Decision Pathway (ECDP) on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk (2022 ACC nonstatin ECDP)[4] was published in response to 3 new nonstatin medications gaining FDA approval (bempedoic acid, evinacumab, and inclisiran). The 2022 ACC nonstatin ECDP supplements the 2018 guideline, providing prescribing recommendations for nonstatin agents in patients with inadequate response to statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs), filling the gaps until the evidence-based guidelines are updated and published. Threshold levels within the 2022 ACC nonstatin ECDP are not considered firm and should be taken into consideration along with the individual patient's entire clinical picture when deciding whether to add nonstatin therapies for further LDL reduction. The section below describes the 4 patient management groups and pharmacotherapy options when further LDL-C reduction is needed.

Box 1 Patient Groups for the Management of Hypercholesterolemia

1. Adults aged ≥ 20 years with clinical ASCVD on statin therapy for secondary prevention
2. Adults aged ≥ 20 years with LDL-C ≥ 190 mg/dL (not due to secondary modifiable causes) on statin therapy for primary prevention
3. Adults aged 40-75 years without ASCVD, but with diabetes and LDL-C < 190 mg/dL, on statin therapy for primary prevention
4. Adults aged 40-75 years without clinical ASCVD or diabetes, with LDL-C 70 to 189 mg/dL and an estimated 10-year risk for ASCVD ≥ 7.5%, on statin therapy for primary prevention

Patient group 1: Adults with clinical ASCVD on statin therapy for secondary prevention.[4]
Previous guidance defines patient group 1 as adults with clinical ASCVD on statin therapy for secondary prevention. Patients with acute coronary syndrome (ACS), history of MI, stable/ unstable angina, coronary or arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) are defined as having clinical ASCVD. ASCVD is broken down into 2 subgroups: patients not at very high risk and patients at very high risk. Very high-risk patients have either a history of multiple ASCVD events or 1 occurrence of an ASCVD event and multiple high-risk conditions which are defined in Table 1.[4]

Patient group 1: Adults with clinical ASCVD at *very high risk* on statin therapy for secondary prevention.[4]
Adults with clinical ASCVD at *very high risk* should receive maximally tolerated statin therapy for secondary prevention. If there is a ≥ 50% reduction in LDL-C from baseline and the LDL-C is < 55mg/dL (or non-high-density lipoprotein (HDL-C) < 85 mg/dL), it is recommended to continue maximally tolerated statin therapy and monitor. If there is a need for further LDL reduction (< 50% reduction in LDL-C and LDL-C is ≥ 55 mg/dL, or non-HDL-C ≥ 85 mg/dL) in patients receiving maximally tolerated statin therapy, nonstatin therapy can be considered. Based on clinical trials IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk), and ODYSSEY (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), first line nonstatin therapy should either be ezetimibe or a PCSK9 mAb.[4] It should be noted that alirocumab and evolocumab were previously referred to as PCSK9 inhibitors, however, current literature now refers to these medications as PCSK9 mAbs. Caveats for selecting ezetimibe or a PCSK9 mAb are included in Box 2.[4] All nonstatin therapies for LDL cholesterol lowering are listed in Table 2.

If there is a need for further LDL reduction (< 50% reduction in LDL-C and LDL-C is ≥ 55 mg/dL, or non-HDL-C ≥ 85 mg/dL) in patients re-

TABLE 1 Criteria for Defining Patients at Very High Risk* of Future ASCVD Events

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)
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 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

*Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. Reprinted with permission from Grundy et al.[7]

ABI = ankle-brachial index; ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral artery disease

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ceiving maximally tolerated statin therapy after the addition of a single agent nonstatin medication, another nonstatin agent may be considered (ezetimibe plus PCSK9 mAb). If there is a need for further LDL reduction < 50% reduction in LDL-C and LDL-C is ≥ 55 mg/dL, or non-HDL-C ≥ 85 mg/dL) in patients receiving maximally tolerated statin therapy, ezetimibe, and a PCSK9 mAb, concurrent therapy with bempedoic acid can be considered. Patients who continue to have a (< 50% reduction in LDL-C and LDL-C is ≥ 55 mg/dL, or non-HDL-C ≥ 85 mg/dL on multiple therapies should be referred to a lipid specialist.

Box 2[1] – First line nonstatin therapy caveats

Caveats for adding ezetimibe:

- Looking for < 25% additional LDL lowering
- Patients with ACS < 3 months
- Lower cost
- Patient preferers oral therapy

Caveats for adding a PCSK9 mAb:

- Looking for > 25% additional LDL lowering
- Subcutaneous (SC) administration, 2x monthly/ monthly
- Higher cost (~$4500/year)
- Storage considerations - must be refrigerated

Due to the published clinical trial information for the PCSK9 mAbs, these medications are preferred over the PCSK9 inhibitor Inclisiran. While there are no current clinical outcomes regarding Inclisiran yet, the ORION-4 (A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People with Cardiovascular Disease) and VICTORION-2P (Impact Of Inclisiran on Major Adverse Cardiovascular Events in Participants with Established Cardiovascular Disease 2 Prevent) outcomes are expected in 2026 and 2027.[2] When considering the addition of Inclisiran as a nonstatin therapy in patients who require further reduction of LDL-C, it should be added in place of a PCSK9 mAb, not to be used concurrently. Inclisiran is administered twice-yearly and may benefit patients who are non-adherent to a PCSK9 mAb.

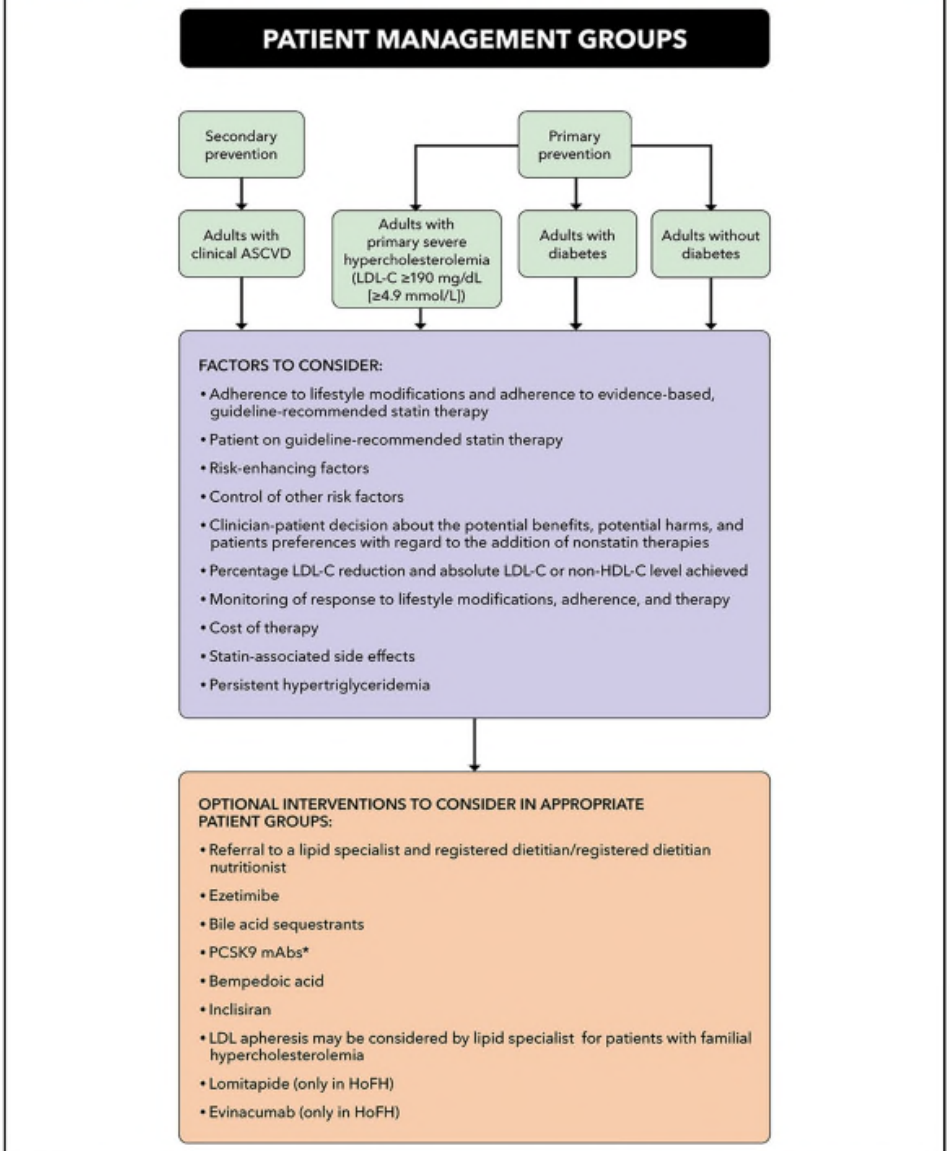
Patient group 1: Adults with clinical ASCVD *not at very high risk* on statin therapy for secondary prevention.[4]

Adults with clinical ASCVD *not at very high risk* should receive maximally tolerated statin therapy for secondary prevention. If there is a ≥ 50% reduction in LDL-C from baseline measurement and the LDL-C is < 70 mg/dL (or non-HDL-C < 100 mg/dL), it is recommended to continue maximally tolerated statin therapy and monitor. If there is a need for further LDL reduction (< 50% reduction in LDL-C and LDL-C is ≥ 70 mg/dL, or non-HDL-C ≥ 100 mg/dL) in patients receiving maximally tolerated statin therapy, nonstatin therapy can be considered. First line nonstatin therapy should either be ezetimibe or a PCSK9 mAb. If there is a need for further LDL reduction (< 50% reduction in LDL-C and LDL-C is ≥ 70 mg/dL, or non-HDL-C ≥ 100 mg/dL) in patients receiving maximally tolerated statin therapy after the addition of a single agent nonstatin medication, another nonstatin agent may be considered (ezetimibe plus PCSK9 mAb). If there is a need for further LDL reduction (< 50% reduction in LDL-C and LDL-C is ≥ 70 mg/dL, or non-HDL-C ≥ 100 mg/dL) in patients receiving maximally tolerated statin therapy, ezetimibe, and a PCSK9 mAb, concurrent therapy with bempedoic acid can be considered. PCSK9 mAbs are preferred over Inclisiran. Inclisiran may be considered in place of a mAb in patients who are non-adherent or intolerant. Patients who continue to have a < 50% reduction in LDL-C and LDL-C is ≥ 70 mg/dL, or non-HDL-C ≥ 100 mg/dL despite multiple therapies should be referred to a lipid specialist.

Patient group 2: Adults with clinical ASCVD and baseline LDL-C ≥ 190 mg/dL not due to secondary causes, on statin therapy for secondary prevention.[4]

Adults with clinical ASCVD and baseline LDL-C ≥ 190 mg/dL not due to secondary causes should receive maximally tolerated statin therapy and genetic testing to rule out familial hypercholesterolemia (FH).

FIGURE 1 Summary Graphic: Patient Populations Addressed and Factors and Interventions to Consider



*PCSK9 mAb includes alirocumab and evolocumab. ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 mAb = proprotein convertase subtilisin/kexin type 9 monoclonal antibodies.

Table 2 Nonstatin Therapies for LDL Cholesterol Lowering [4, 5-11]

Medication	Indication	Common Dosage	Adverse Drug Effects (ADEs)	Mean % LDL Reduction	Clinical Pearls
NPC1L1 inhibitor, reduces the absorption of cholesterol from the small intestine					
Ezetimibe (Zetia)	1. Primary Hyperlipidemia 2. HoFH 3. Homozygous Sitosterolemia	10 mg/day	Elevated LFTs, rhabdomyolysis/myopathy, arthralgias.	17% - 25%	Not recommended in hepatic impairment, available as a combination product with statin, Pregnancy category C.
PCSK9 mAb, inhibits PCSK9 extracellularly increasing LDL receptors and decreasing LDL					
Alirocumab (Praluent)	1. Adults with established CVD 2. Primary hyperlipidemia, including HeFH 3. HoFH	75-300 mg SC Q 2 weeks	Injection site reactions, diarrhea, risk of hypersensitivity reactions	45 - 58%	Requires refrigeration, cost has declined in recent years, not to use concurrently with the PCSK9i Inclisiran
Evolocumab (Repatha)	1. In adults with established CVD 2. Primary hyperlipidemia, including HeFH 3. Pediatric patients aged 10 years and older with HeFH 4. Adults and pediatric patients aged 10 years and older with HoFH	Primary hypercholesterolemia/ HeFH 140 mg SC Q 2 weeks or 420 mg SC Q month HoFH 420 mg SC Q month and may increase to 420 SC Q 2 weeks	Injection site reactions. Diarrhea. Risk of hypersensitivity reactions	58 - 64%	Requires refrigeration, cost has declined in recent years, not to use concurrently with the PCSK9i Inclisiran
PCSK9 Inhibitor, siRNA that inhibits the production of PCSK9 intracellularly (rather than extracellularly as the PCSK9 mAbs do), maximizing LDL receptor longevity					
Inclisiran (Leqvio)	1. Primary hyperlipidemia, including HeFH	284 mg SC initially and again at 3 months and then every 6 months thereafter.	Injection site reactions, development of antidrug antibodies	48 - 52%	Not to use concurrent with PCSK9 mAb, in general there are no drug-drug interactions associated, preferred over mAb in patients with adherence issues, administered twice a year but must be administered by a health care professional, CV outcomes trials are still not completed
ACLY Inhibitor, improves clearance of and decreases blood LDL while increasing LDL receptors and blocking synthesis of cholesterol in the liver					
Bempedoic Acid (Nexletol)	1. Primary hyperlipidemia, including HeFH	180 mg/day (oral)	Tendon rupture, gout (increase in serum uric acid levels), BPH, Afib, and elevation of creatine kinase	17-18%	Bempedoic acid is a prodrug and activated by an enzyme (coenzyme A) found in the liver and not in muscle cells and therefore does not affect muscles the way statins do. Comes as a combination product with ezetimibe. Not recommended to use with simvastatin doses > 20 mg/day or pravastatin doses > 40 mg/day.
ANGPTL3 Inhibitor, recombinant human monoclonal antibody that reduces LDL while promoting VLDL processing and clearance upstream of LDL formation					
Evinacumab (Evkeeza)	1. Adult and pediatric patients, aged 5 years and older with HoFH	15 mg/kg IV infusion once monthly	Infusion related reactions, nasopharyngitis, flu like symptoms	49%	Good option for severe hypertriglyceridemia, recommended for patients of child bearing potential to use contraception during treatment and for 5 months after the last dose due to associated fetal toxicity.
MTP Inhibitor, inhibits the synthesis of VLDL in the liver, thereby decreasing the LDL					
Lomitapide (Juxtapid)	1. Adult patients with HoFH	5 mg/day (oral) titrating up after 2 weeks up to a max dose of 60 mg/day. Max dose of 30 mg/day when concomitant with weak 3A4 inhibitors (atorvastatin or oral contraceptives)	90% of patients experience gastrointestinal (GI) side effects - diarrhea, nausea, vomiting. 30% of patients experience increase in LFTs	40%	Titrate slowly and reduce dietary fat intake to avoid severity of GI ADEs. Recommend dietary supplements of fat-soluble vitamins (vitamin E, linoleic acid, alpha-linolenic acid , eicosatetraenoic acid , docosahexaenoic acid). Prescriber training, REMS, and monitoring of LFTs is required. Contraindicated in pregnancy, concurrent use with moderate/strong 3A4 inhibitors, and moderate/severe hepatic impairment. Should be administered with concurrent LDL apheresis where available.
LDL Apheresis, process similar to dialysis where blood is removed from patient's vein in order to remove cholesterol from the blood					
LDL Apheresis	Patients with FH who are unresponsive to dietary and pharmacological therapy with an LDL > 500 mg/dL, functional heterozygotes without CV disease with an LDL > 300 mg/dL, or functional heterozygotes with CVD and an LDL > 200	Procedure is performed once or twice weekly	Hypotension, fatigue, bleeding. Bradykinin syndrome can develop in patients receiving concurrent ACEi	50 - 60% There is LDL rebound post procedure but not back to baseline.	Expensive, time consuming, and not always available in rural areas

NPC1L1=Niemann-Pick C1-Like 1; PCSK9 mAb=Proprotein convertase subtilisin/kexin type 9 monoclonal antibody; HoFH=Homozygous Familial Hypercholesterolemia; LDL=low density lipoproteins; LFTs=liver function tests; CVD=cardiovascular disease; HeFH=heterozygous familial hypercholesterolemia; siRNA=small interfering ribonucleic acid; SC=subcutaneous; ACLY=ATP-citrate lyase; ANGPTL3=Angiopoietin-Like Protein 3; IV=intravenous; MTP=Microsomal triglyceride transfer protein; BPH=Benign prostatic hyperplasia; Afib=atrial fibrillation; VLDL=very low-density lipoprotein; GI=gastrointestinal; REMS=Risk Evaluation and Mitigation Strategy;

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Those not diagnosed with FH follow a similar treatment plan for patients with clinical ASCVD, who are not at very high risk. If there is a ≥ 50% reduction in LDL-C from baseline measurement and the LDL-C is < 70 mg/dL (or non-HDL-C < 100 mg/dL), it is recommended to continue maximally tolerated statin therapy and monitor. If there is a need for further LDL reduction (< 50% reduction in LDL-C and LDL-C is ≥ 70 mg/dL, or non-HDL-C ≥ 100 mg/dL) in patients receiving maximally tolerated statin therapy, nonstatin can be considered. First line nonstatin therapy should either be ezetimibe or a PCSK9 mAb. If there is a need for further LDL reduction (< 50% reduction in LDL-C and LDL-C is ≥ 70 mg/dL, or non-HDL-C ≥ 100 mg/dL) in patients receiving maximally tolerated statin therapy after the addition of a single agent nonstatin medication, another nonstatin agent may be considered (ezetimibe plus PCSK9 mAb). If there is a need for further LDL reduction (< 50% reduction in LDL-C and LDL-C is ≥ 70 mg/dL, or non-HDL-C ≥ 100 mg/dL) in patients receiving maximally tolerated statin therapy, ezetimibe, and a PCSK9 mAb, concurrent therapy with bempedoic acid can be considered. PCSK9 mAb are preferred over Inclisiran. Inclisiran may be considered in place of a mAb in patients who are non-adherent or intolerant. Patients who continue to have a < 50% reduction in LDL-C and LDL-C is ≥ 70 mg/dL, or non-HDL-C ≥ 100 mg/dL on multiple therapies should be referred to a lipid specialist. Any patient who presents with clinical ASCVD and LDL-C ≥ 200 mg/dL, who are not diagnosed with FH may be eligible for LDL apheresis but would need a specialist to guide care.

ASCVD patients with a diagnosis of FH and an LDL-C ≥ 190 mg/dL are considered high risk patients. Patient diagnosed with homozygous familial hypercholesterolemia (HoFH) should receive statins, and/or ezetimibe/PCSK9 mAb and should consider adding evinacumab or lomitapide if there is < 50% reduction in LDL-C or if LDL-C ≥ 55 mg/dL. Patients diagnosed with heterozygous familial hypercholesterolemia (HeFH) or HoFH who have a substandard response to statin/ezetimibe/PCSK9 mAb therapy are also candidates for LDL apheresis.

Patient group 2: Adults *without* clinical ASCVD and with baseline LDL-C ≥ 190 mg/dL not due to secondary causes, on statin therapy for primary prevention.[4]

Adults *without* clinical ASCVD and baseline LDL-C ≥ 190 mg/dL not due to secondary causes should receive maximally tolerated statin therapy, referral to a lipid specialist, and genetic testing to rule out familial hypercholesterolemia (FH). Those not diagnosed with FH follow a similar treatment plan for patients with clinical ASCVD. If there is a ≥ 50% reduction in LDL-C from baseline measurement and the LDL-C is < 100 mg/dL (or non-HDL-C < 130 mg/dL), it is recommended to continue maximally tolerated statin therapy and monitor. If there is a need for further LDL reduction (< 50% reduction in LDL-C and LDL-C is ≥ 100 mg/dL, or non-HDL-C ≥ 130 mg/dL) in patients receiving maximally tolerated statin therapy, a nonstatin can be considered. First line nonstatin therapy should either be ezetimibe or a PCSK9 mAb. If there is a need for further LDL reduction (< 50% reduction in LDL-C and LDL-C is ≥ 100 mg/dL, or non-HDL-C ≥ 130 mg/dL) in patients receiving maximally tolerated statin therapy after the addition of a single agent nonstatin medication, another nonstatin agent may be considered (ezetimibe plus PCSK9 mAb). If there is a need for further LDL reduction (< 50% reduction in LDL-C and LDL-C is ≥ 100 mg/dL, or non-HDL-C ≥ 130 mg/dL) in patients receiving maximally tolerated statin therapy, ezetimibe, and a PCSK9 mAb, concurrent therapy with bempedoic acid can be considered. PCSK9 mAbs are preferred over Inclisiran. Inclisiran may be considered in place of a mAb in patients who are non-adherent or intolerant. Patients who continue to have a < 50% reduction in LDL-C and LDL-C is ≥ 100 mg/dL, or non-HDL-C ≥ 130 mg/dL on multiple therapies should consult with their lipid specialist to discuss options such as evinacumab, lomitapide, and LDL apheresis.

Patient group 2: Adults With LDL-C ≥ 190 mg/dL With or Without Concomitant ASCVD Risk Factors.[4]

Adults with LDL-C ≥ 190 mg/dL with or without concomitant ASCVD risk factors will follow the same pathway as adults *without* clinical ASCVD and baseline LDL-C ≥ 190 mg/dL not due to secondary causes (above). These patients may or may not have concomitant ASCVD risk factors such as family history, tobacco use, diabetes, hypertension, or chronic kidney disease.

Patient group 3: Adults with diabetes and without ASCVD and baseline LDL-C < 190 mg/dL on statin therapy for primary prevention.[4]

Adults with diabetes and without ASCVD and baseline LDL-C < 190 mg/dL on statin therapy for primary prevention should undergo assessment of 10-year ASCVD risk. If the predicted 10-year risk is <7.5%, it is recommended these patients receive moderate statin therapy. If there is inadequate response to moderate therapy (<30-49% reduction in LDL-C or LDL-C ≥ 100 mg/dL or non-HDL-C ≥ 130 mg/dL, statin therapy can be intensified. If there is a need for further LDL reduction (< 50% reduction in LDL-C and LDL-C is ≥ 100 mg/dL, or non-HDL-C ≥ 130 mg/dL) in patients receiving maximally tolerated statin therapy, ezetimibe can be considered. PCSK9 mAb, bempedoic acid, and inclisiran are not recommended for use in diabetic patients without ASCVD and a baseline LDL < 190 mg/dL.

Patient group 4: Adults without clinical ASCVD or diabetes (LDL 70-189 mg/dL).[4]

Adults without clinical ASCVD or diabetes and LDL 70-189 mg/dL should undergo assessment of 10-year ASCVD risk. If the predicted 10-year risk is ≥7.5% it is recommended these patients receive statin therapy. If there is a need for further LDL reduction in patients receiving maximally tolerated statin therapy, ezetimibe can be considered. PCSK9 mAb, bempedoic acid, and inclisiran are not recommended for use in this patient population.

Statins have remained and continue to be the foundation for pharmacotherapy management of dyslipidemia, however, treatment options are expanding and evolving. Understanding the role of nonstatin medications in patients who have an inadequate response to first line therapy is crucial for the management of this chronic disease. Data shows that more than ½ of US adults with dyslipidemia do not receive appropriate care which can result in future ASCVD events, increased costs, and patient morbidity and mortality. Guidelines and expert consensus pathways exist to help providers select treatment options for patients with this disease, however, the intent is not meant to take the place of clinical judgement. When considering the addition of a nonstatin medication, providers should account for a patient's entire clinical picture and strive to provide individualized care for further LDL reduction.

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