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The 2022 American College of Cardiology Expert Consensus on the Role of Nonstatin Therapies: An Expert-Guided Tour

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Introduction

Cardiovascular disease is the leading cause of death in women in the United States and worldwide. Reducing patients' lifetime exposure to low-density lipoprotein cholesterol (LDL-C) lowers their risk of atherosclerotic cardiovascular disease (ASCVD), as multiple clinical trials and meta-analyses have shown.[1] Every 1.0-mmol/L (38.7-mg/dL) reduction in LDL-C is associated with a 23% relative risk reduction in major ASCVD events.[2] Abundant clinical trial evidence has led to statins becoming the cornerstone of LDL-C–lowering therapy.[3] Although many patients achieve target LDL-C levels with statins, some patients have a suboptimal response stemming from treatment intolerance, genetic differences, treatment nonadherence, or therapeutic inertia. Since the 2013 cholesterol guidelines were published,[4] major advances in nonstatin therapies, including the development and approval of additional agents, have enabled greater LDL-C reduction and expanded treatment options. Clinical trials of more recent nonstatin therapies, including IMPROVE-IT,[5] FOURIER,[6] ODYSSEY OUTCOMES,[7] and CLEAR Outcomes,[8] have provided support for the additional benefits nonstatin therapies and LDL-C reduction provide.[9]

Current Opportunities for Improvement

Nonstatin therapies currently available for reducing LDL-C levels include ezetimibe, bempedoic acid, bile acid–binding resins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and evinacumab (Table I). Ezeti-

TABLE I. Nonstatin Therapy Options: LDL-C–Lowering Efficacy

Agent	LDL-C reduction when combined with statin, %
Ezetimibe	40-50
Bempedoic acid	17-18
Evolocumab, alirocumab	40-60
Inclisiran	48 to 52
Evinacumab	49

LDL-C, low-density lipoprotein cholesterol.

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mibe as monotherapy can reduce LDL-C by 18%, and ezetimibe with statins as combination therapy reduces LDL-C by 50% to 70%. Bempedoic acid as monotherapy provides 24% LDL-C reduction. Bile acid–binding resins used in addition to statins provide a 15% to 27% reduction, although there are no outcome data for this combination. Evolocumab and alirocumab (PCSK9 monoclonal antibodies [mAbs]) are highly effective in reducing LDL-C, doing so by about 60%. Inclisiran, a small interfering RNA against PCSK9, provides 48% to 52% LDL-C reduction when combined with a statin. Evinacumab, a mAb infusion targeting ANGPTL3, is used in patients with homozygous familial hypercholesterolemia, for whom it provides 49% LDL-C reduction.

Recent Developments

In high-risk patients, the goal is an LDL-C level below 1.4 mmol/L (55 mg/dL); levels above that warrant the consideration of additional lipid-lowering therapy. These recommendations are based on FOURIER and ODYSSEY OUTCOMES, 2 trials that demonstrated the cardiovascular outcomes benefits of reducing LDL-C levels. Since the 2018 cholesterol guidelines were released,[10] PCSK9 inhibitors have become more affordable and therefore are increasingly incorporated into clinical practice, which helps patients achieve these target LDL-C levels. In high-risk patients with clinical ASCVD who require greater LDL-C reduction than a single additional therapy can be expected to achieve, it may be reasonable to consider the simultaneous addition of 2 agents to reduce the patient's risk of recurrent events more rapidly. In such cases, combination therapy with high-intensity or maximally tolerated statin therapy and ezetimibe or maximally tolerated statin therapy with or without ezetimibe and PCSK9 mAbs can be used.[4,9]

Subclinical atherosclerosis assessment can be incorporated into practice for risk assessment and treatment. The coronary artery calcium (CAC) score has been widely incorporated into practice to guide lipid-lowering therapy because it is a powerful prognostic indicator of future events. For individuals with a CAC score (also called the Agatston score) of 0 in the absence of diabetes, an LDL-C level of 4.9 mmol/L (190 mg/dL) or higher, a family history of premature coronary heart disease, or active cigarette smoking, it is reasonable to defer statin therapy and reassess CAC in 3 to 5 years while focusing on lifestyle modifications. For individuals with a CAC score of 1 to 99 who are in less than the 75th percentile for their age and sex, moderate-intensity statin therapy is reasonable. In the Multi-Ethnic Study of Atherosclerosis, individuals with a CAC score higher than 100 or who were in at least the 75th percentile had a 10-year incidence rate of hard ASCVD events of more than 7.5%, a data point that supports the initiation of moderate- or high-intensity statin therapy. Titration to high-intensity statin therapy may be considered if the patient achieves less than 30% LDL-C reduction or their LDL-C remains at 2.6 mmol/L (100 mg/dL) or higher. Patients with CAC scores of at least 1,000 who are not on statin therapy have high annual clinical ASCVD event rates (3.3 per 100 person-years). If the patient is already on statin/ezetimibe therapy, addition of a PCSK9 mAb may be considered for LDL-C reduction.

Abbreviations and Acronyms

ASCVD	atherosclerotic cardiovascular disease
CAC	coronary artery calcium
LDL-C	low-density lipoprotein cholesterol
mAb	monoclonal antibody
PCSK9	proprotein convertase subtilisin/kexin type 9

Future Directions

Achieving optimal LDL-C levels is challenging in patients with statin intolerance, a condition that occurs more often in women.[10] Since the 2022 Expert Consensus Decision Pathway on nonstatin therapy recommendations was published, CLEAR Outcomes, which enrolled approximately 50% female participants, showed that bempedoic acid effectively reduced LDL-C levels compared with placebo and that it reduced major adverse cardiovascular events.[8] The ongoing ORION-4 trial is examining the effects of inclisiran on cardiovascular events in patients with ASCVD. Agents in development and currently undergoing clinical trials include an oral PCSK9 inhibitor and lipoprotein(a)-targeting therapies.

Despite all available therapies, many patients do not achieve optimal LDL-C levels because of changes in guidelines, competing comorbidities and polypharmacy, statin intolerance, cost issues, and treatment nonadherence. Combination therapy with nonstatin agents, medication titration to achieve LDL-C goals, and the close monitoring of LDL-C levels will help provide greater LDL-C reduction and a greater reduction in clinical events.

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