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Authors

Wilkinson, Michael
Lepor, Norman
Michos, Erin

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CONTEMPORARY REVIEW

Evolving Management of Low-Density Lipoprotein Cholesterol: A Personalized Approach to Preventing Atherosclerotic Cardiovascular Disease Across the Risk Continuum

Michael J. Wilkinson, MD; Norman E. Lepor, MD; Erin D. Michos, MD, MHS

ABSTRACT: Management of elevated low-density lipoprotein cholesterol (LDL-C) is central to preventing atherosclerotic cardiovascular disease (ASCVD) and key to reducing the risk of ASCVD events. Current guidelines on the management of blood cholesterol recommend statins as first-line therapy for LDL-C reduction according to an individual's ASCVD risk and baseline LDL-C levels. The addition of nonstatin lipid-lowering therapy to statins to achieve intensive LDL-C lowering is recommended for patients at very high risk of ASCVD events, including patients with familial hypercholesterolemia who have not achieved adequate LDL-C lowering with statins alone. Despite guideline recommendations and clinical trial evidence to support the use of lipid-lowering therapies for ASCVD risk reduction, most patients at high or very high risk do not meet LDL-C thresholds. This review explores the challenges associated with LDL-C lowering in contemporary clinical practice and proposes a framework for rethinking the binary definition of ASCVD, shifting from "primary" versus "secondary" prevention to a "continuum of risk." The approach considers the role of plaque burden and progression in subclinical disease and emphasizes the importance of early risk assessment and treatment for preventing first cardiovascular events. Patients at high risk of ASCVD events who require significant LDL-C lowering should be considered for combination therapies comprising statin and nonstatin agents. Practical guidance for the pharmacological management of elevated LDL-C, both now and in the future, is provided.

Key Words: atherosclerosis ■ atherosclerotic cardiovascular disease ■ lipids ■ low-density lipoprotein cholesterol ■ prevention

Low-density lipoprotein cholesterol (LDL-C) is a major causal factor in the pathophysiology of atherosclerotic cardiovascular disease (ASCVD).[1] Epidemiological studies have consistently demonstrated a dose-dependent log-linear relationship between plasma LDL-C concentrations and risk of ASCVD events; this relationship is replicated in Mendelian randomization studies.[1] In addition to the magnitude of LDL-C exposure, long-term exposure to persistently elevated LDL-C is recognized as a key contributor to a person's ASCVD risk.[2]

Management of LDL-C levels is central to ASCVD prevention strategies, beginning with the recommendation of a heart-healthy lifestyle for all individuals.[3] In those at increased ASCVD risk, pharmacologic lipid-lowering therapy is advocated, with statin therapy recommended as the first-line agent for both primary and secondary prevention. However, for many high-risk patients with elevated LDL-C, individuals with familial hypercholesterolemia (FH), and/or those who have limiting statin-associated adverse effects, nonstatin therapies as part of a multidrug regimen are often needed to achieve LDL-C thresholds.

Correspondence to: Michael J. Wilkinson, MD, Division of Cardiovascular Medicine, Department of Medicine, Cardiovascular Institute, University of California San Diego, 9434 Medical Center Dr #7214, La Jolla, CA 92037. Email: mjwilkinson@health.ucsd.edu

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Nonstandard Abbreviations and Acronyms

ACC	American College of Cardiology
AHA	American Heart Association
CETP	cholesteryl ester transfer protein
EAS	European Atherosclerosis Society
ECDP	Expert Consensus Decision Pathway
ESC	European Society of Cardiology
FH	familial hypercholesterolemia
HeFH	heterozygous familial hypercholesterolemia
PCSK9	proprotein convertase subtilisin/kexin type 9

Pooled analyses of lipid-lowering therapies have shown a linear association between achieved LDL-C levels and absolute coronary heart disease event rates.[4] Every 1.0-mmol/L (39-mg/dL) reduction in LDL-C confers an ≈22% reduction in the risk of major vascular events, with the lower threshold beyond which benefit ceases yet to be defined.[4–6] Nonstatin lipid-lowering therapies to assist with LDL-C reduction are now available. Current American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety and European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines recommend the addition of ezetimibe and/or anti-PCSK9 (proprotein convertase subtilisin/kexin type 9) monoclonal antibodies to statins in individuals who require further LDL-C lowering according to the level of risk.[3,5] Since the publication of the most recent guidelines, bempedoic acid, an ATP-citrate lyase inhibitor, and inclisiran, a small interfering RNA that targets PCSK9 mRNA, have received regulatory approval for LDL-C lowering in combination with statins,[7,8] with pending cardiovascular outcome studies in the case of inclisiran. To acknowledge these new nonstatin lipid-lowering therapies, in 2022, the ACC published an Expert Consensus Decision Pathway (ECDP) statement to provide guidance on their use across various ASCVD risk groups.[6]

Despite guideline recommendations and evidence supporting the use of lipid-lowering therapies for ASCVD risk reduction, recent population studies indicate that their current use for preventing ASCVD events is insufficient. Most patients at high or very high risk do not meet LDL-C thresholds. Long-term adherence and persistence with statin therapy are poor, even following a catastrophic event, such as acute myocardial infarction.[9–14] Consequently, in patients who fall within established benefit groups according to current guidelines, there is a significant need to increase the use of available lipid-lowering therapies, especially statins, at the recommended intensity.

Current guidelines categorize recommendations for the pharmacological management of elevated LDL-C by primary and secondary prevention of ASCVD events[3,5,15]; however, as demonstrated by tools for imaging coronary atherosclerosis (including coronary artery calcium [CAC] scoring, coronary computed tomographic angiography, intravascular ultrasound, and optical coherence tomography), a continuum of ASCVD and associated risk exists.[16,17] Patients are at increased risk as both plaque burden and high-risk plaque features accumulate before their first ASCVD event.[18] Intensive LDL-C lowering is therefore critical to halt plaque progression, with the potential to induce regression and prevent outcomes, such as myocardial infarction, cerebrovascular accident, or the need for coronary revascularization. This concept is recognized in the 2019 ESC/EAS guideline, which considers unequivocal evidence of ASCVD on imaging as very high risk, the same category as those with documented ASCVD events.[5]

Multiple challenges exist to effective LDL-C management in patients with, and at risk for, ASCVD (Figure 1). This review presents a framework for rethinking the binary definition of ASCVD, shifting from primary versus secondary prevention to a continuum of risk. Such an approach acknowledges the role of plaque burden and progression in subclinical disease and emphasizes the importance of early risk assessment and treatment to prevent first cardiovascular events (ie, "high-risk primary prevention").

DEFINING RISK: THE CONTINUUM OF ASCVD RISK

Current Guideline Recommendations for Risk Estimation

Assessment of baseline and residual ASCVD risk is the foundation of preventive cardiology. Guidelines recommend defining LDL-C treatment thresholds and enabling the appropriate selection of individuals who might derive a net benefit from lipid-lowering therapy.[3,5,15,19] Global risk scores are the first step in risk estimation but have limitations, including limited representation of certain racial and ethnic groups and a focus solely on selected traditional risk factors. For instance, current models may overestimate risk in East Asian patients and underestimate risk in South Asian patients.[19,20] In addition, risk scores may overestimate risk in patients with higher socioeconomic status and underestimate risk in those from socially disadvantaged backgrounds.[16] Risk scores are also not applicable in patients with FH or baseline LDL-C ≥190 mg/dL because of the inherent higher lifetime risk of ASCVD events.[19] Beyond traditional risk factors, assessment of other risk-enhancing factors, including lipoprotein(a),

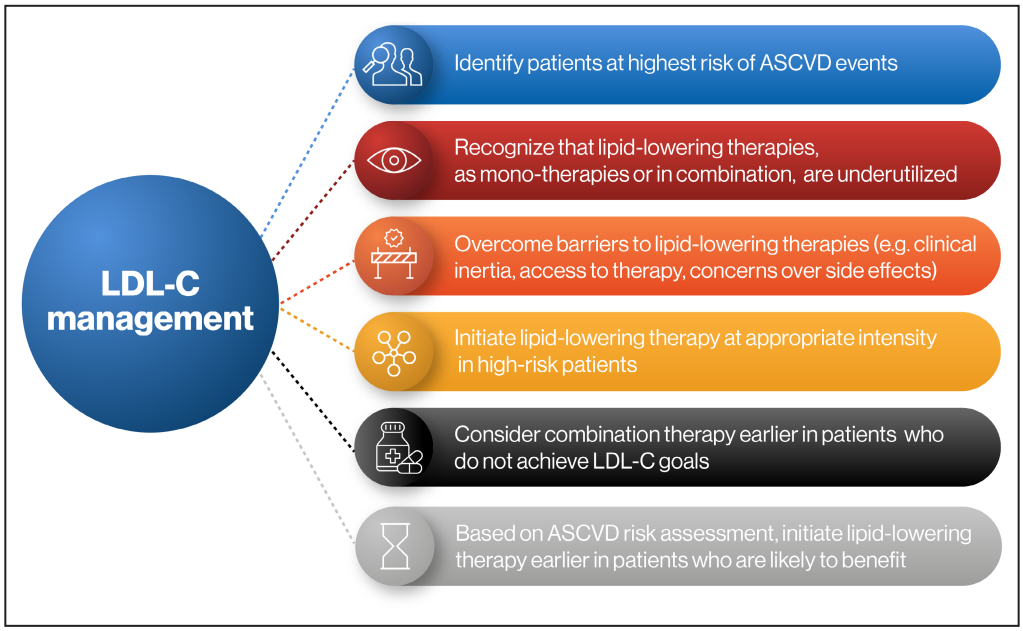

Figure 1. Challenges to low-density lipoprotein cholesterol (LDL-C) management in patients with, and at risk for, atherosclerotic cardiovascular disease (ASCVD).

chronic kidney disease, chronic inflammatory conditions, family history of premature ASCVD, history of premature menopause, and subclinical atherosclerosis, can further refine risk estimation (Figure 2),[3,5,15,16] but these are often not adequately captured in traditional scoring models.[21,22]

For adults 40 to 75 years of age, the 2018 ACC/AHA/Multisociety guideline on cholesterol management and 2019 ACC/AHA guideline on primary prevention recommend estimation of 10-year absolute ASCVD risk (myocardial infarction and stroke, both fatal and nonfatal) by using the race- and sex-specific US-derived pooled cohort equations.[3,15] Additional risk-enhancing factors may guide clinical decision-making in individuals at borderline (5% to <7.5% 10-year ASCVD risk) or intermediate risk (≥7.5% to <20% 10-year ASCVD risk), and measurement of CAC is recommended if risk-based treatment decisions remain uncertain in such individuals.

The 2019 ESC/EAS guideline recommends using the Systematic Coronary Risk Estimation system, based on large, European cohort data sets, for estimating the 10-year risk of fatal ASCVD events in adults >40 years of age.[5] The Systematic Coronary Risk Estimation tool has since been updated as Systematic Coronary Risk Estimation 2, which predicts 10-year risk for both fatal and nonfatal ASCVD events.[23] Also, CAC scoring is recommended in asymptomatic individuals classified as low or intermediate risk for whom statin therapy is being considered.[5] A summary of the risk categories and recommendations for LDL-C lowering in both the ACC/AHA/Multisociety and ESC/EAS guidelines is provided in Table 1.[3,5]

Both the US and European guidelines recommend consideration of nonstatin lipid-lowering therapy in addition to statins for patients at very high risk of ASCVD events; however, the guidelines differ in their respective definitions of patients at "very high risk."[3,5] In the ACC/AHA/Multisociety guidelines, patients with a history of multiple major ASCVD events or those who have had one major ASCVD event plus multiple high-risk conditions are considered very high risk. Recommendation for add-on nonstatin therapy is therefore restricted to secondary prevention for patients at an LDL-C threshold of ≥70 mg/dL.[3] The ESC/EAS guideline adopts a broader definition of very high risk, encompassing those with documented ASCVD, either clinical or unequivocal on imaging or various other higher-risk conditions in the absence of ASCVD. A more aggressive approach to lipid lowering is advocated. Add-on nonstatin therapies are recommended if a target reduction of ≥50% in LDL-C values from baseline and a treatment goal of <55 mg/dL are not achieved.[5]

The 2022 ACC ECDP on the role of nonstatin therapies in ASCVD risk reduction includes a discussion of the newer agents (bempedoic acid, evinacumab, and inclisiran) approved for LDL-C lowering since the publication of the latest guidelines.[6] In patients with clinical ASCVD at very high risk, the addition of nonstatin therapy is recommended if LDL-C levels remain ≥55 mg/dL, in view of the favorable net clinical benefit. In patients with clinical ASCVD who are not at very high risk, a ≥50% reduction in LDL-C from baseline and a threshold of LDL-C <70 mg/dL is considered a desirable response to lipid-lowering therapy.

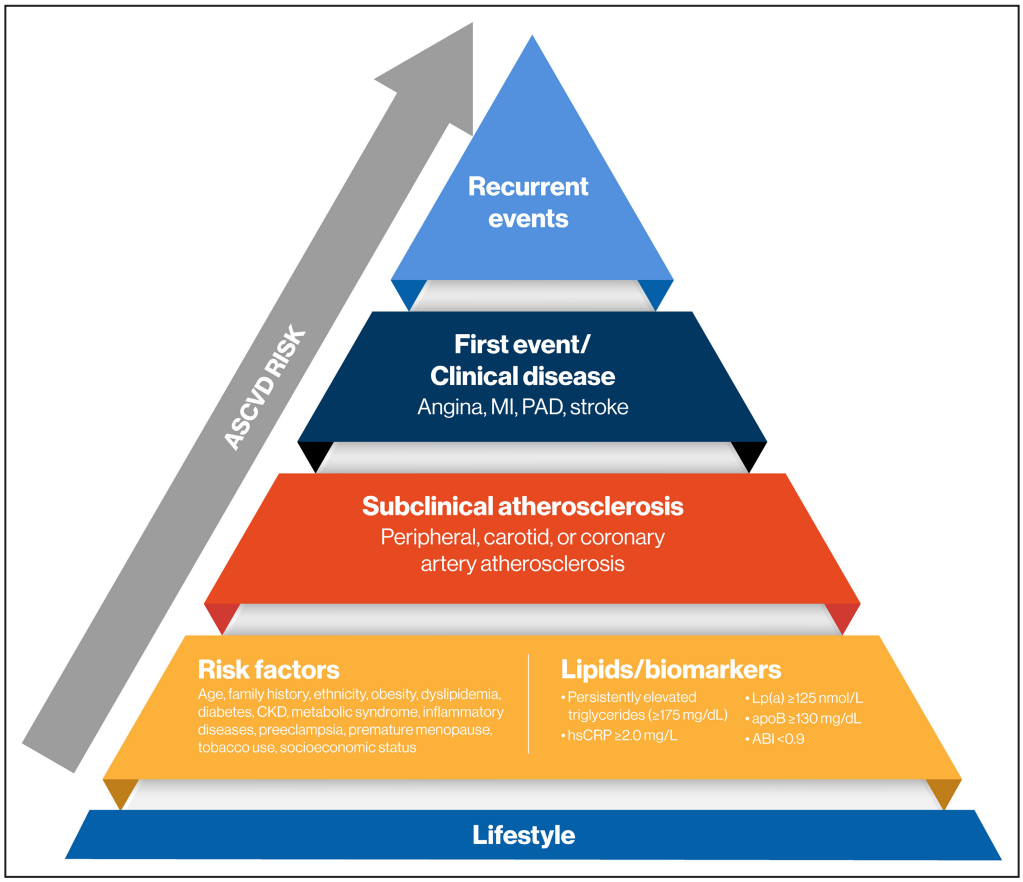

Figure 2. Risk factors and progression along the continuum of atherosclerotic cardiovascular disease (ASCVD).[3,5,15,16]
ABI indicates ankle-brachial index; apoB, apolipoprotein B; CKD, chronic kidney disease; hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein(a); MI, myocardial infarction; and PAD, peripheral arterial disease.

Estimating the Risk of Recurrent ASCVD Events

Patients with established ASCVD are at very high risk for future events; however, this population has substantial variation in the degree of risk.[24] The Secondary Manifestations of ARTerial disease risk score was developed to predict the 10-year risk of recurrent vascular events, identifying patients who are most likely to benefit from treatment intensification and facilitating a personalized approach to secondary prevention.[25] Originally developed from the Utrecht Cardiovascular–Secondary Manifestations of ARTerial disease cohort, the tool has recently been updated with regional incidence rates, broadening its applicability across European and non-European populations.[26]

The Role of Other Atherogenic Lipids

Beyond LDL-C, elevated levels of other atherogenic lipids contribute to an individual's ASCVD risk. For example, elevated lipoprotein(a) is a genetically determined, independent, causal risk factor for ASCVD.[27] Current AHA/ACC/Multisociety guidelines recommend consideration of a lipoprotein(a) level ≥50 mg/dL (or ≥125 nmol/L) if measured as a risk-enhancing factor to guide statin initiation in those at borderline or intermediate risk of ASCVD events.[3] Guidance on how to incorporate lipoprotein(a) concentration into a person's 10-year ASCVD risk has also recently been provided within a statement from the AHA.[27] Statins do not lower lipoprotein(a) and, in some studies, have been associated with increased lipoprotein(a) levels among recipients.[27] Consequently, clinicians should be aware that elevated lipoprotein(a) remains an important contributor to ASCVD risk in the setting of LDL-C lowering with statins.

In addition to lipoprotein(a), triglyceride-rich lipoproteins (which are reflected in measures such as non–high-density lipoprotein cholesterol and remnant cholesterol) contribute to lipid-related risk for ASCVD.[3,28] Persistent elevations of triglycerides ≥175 mg/dL are recognized as a risk-enhancing factor in the AHA/ACC/Multisociety guidelines.[3]

Table 1. Classification of ASCVD Risk and LDL-C Thresholds Defined by US and European Guidelines

Variable	2018 ACC/AHA/multisociety guidelines[3]	2019 ESC/EAS guideline[5]
Risk assessment	Pooled cohort equations	SCORE system
Risk stratification cohorts		
Low risk	10-y risk for ASCVD <5%	Calculated SCORE<1% for 10-y risk of fatal CVD
Borderline, intermediate, or moderate risk	Borderline: 10-y risk for ASCVD 5% to <7.5% Intermediate: 10-y risk for ASCVD ≥7.5% to <20% Consider risk-enhancing factors and CT for CAC scoring in these groups	Moderate risk: • Young patients (T1DM <35 y; T2DM <50 y) with diabetes duration <10 y, without other risk factors • Calculated SCORE ≥1% and <5% for 10-y risk of fatal CVD Consider CT for CAC scoring as a risk modifier
High risk	10-y risk for ASCVD ≥20%	Patients with any of the following: • Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mm Hg • FH without other major risk factors • Diabetes without target organ damage, with diabetes duration ≥10 y or another additional risk factor • Moderate CKD (eGFR 30–59 mL/min per 1.73 m^2) • Calculated SCORE ≥5% and <10% for 10-y risk of fatal CVD
Very high risk	Patients with a history of multiple major ASCVD events: • Recent ACS (within the past 12 mo) • History of MI (other than recent ACS) • History of ischemic stroke • Symptomatic peripheral arterial disease* OR 1 major ASCVD event and multiple high-risk conditions†	Patients with any of the following: • Documented ASCVD‡ either clinical or unequivocal on imaging§ • Diabetes with target organ damage or ≥3 major risk factors or early onset of T1DM of long duration (>20 y) • Severe CKD (eGFR <30 mL/min per 1.73 m^2) • A calculated SCORE ≥10% for a 10-y risk of fatal CVD • FH with ASCVD or with another major risk factor
LDL-C thresholds and recommendations for lipid-lowering therapy		
High-risk cohort	• Maximally tolerated statins to reduce LDL-C by ≥50% from baseline	• A therapeutic regimen to reduce LDL-C by ≥50% from baseline and to achieve LDL-C goal of <70 mg/dL (<1.8 mmol/L)
Very high-risk cohort	• Maximally tolerated statins to reduce LDL-C by ≥50% from baseline • Additional nonstatin therapy (ezetimibe and/or anti-PCSK9 monoclonal antibody) for patients who remain at LDL-C ≥70 mg/dL (≥1.8 mmol/L)	• A therapeutic regimen to reduce LDL-C by ≥50% from baseline and to achieve LDL-C goal of <55 mg/dL (<1.4 mmol/L) or <40 mg/dL (<1.0 mmol/L) in patients who experience a second event in 2 y on statins • Nonstatin therapy (ezetimibe and/or anti-PCSK9 monoclonal antibody) recommended if target reduction of LDL-C ≥50% from baseline and <55 mg/dL (1.4 mmol/L) are not achieved

ACC indicates American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CAC, coronary artery calcium; CKD, chronic kidney disease; CT, computed tomography; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; SCORE, Systemic Coronary Risk Estimation; TC, total cholesterol; T1DM, type 1 diabetes; and T2DM; type 2 diabetes.

*History of claudication with ankle-brachial index <0.85 or previous revascularization or amputation.

†High-risk conditions include age ≥65 years, heterozygous FH, history of coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD events, diabetes, hypertension, CKD (eGFR 15–59 mL/min per 1.73 m^2), current smoking, persistently elevated LDL-C (≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe, and history of congestive heart failure.

‡Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (percutaneous coronary intervention, coronary artery bypass grafting, and other arterial revascularization procedures), stroke and transient ischemic attack, and peripheral arterial disease.

§Unequivocally documented ASCVD includes findings known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with 2 major epicardial arteries with >50% stenosis) or carotid ultrasound.

Assessing CAC

In addition to the assessment of traditional risk factors, there is extensive evidence on the utility of CAC in refining the prediction of vascular events.[29,30] The MESA (Multi-Ethnic Study of Atherosclerosis) 10-year coronary heart disease risk score was the first to include CAC and traditional risk factors and was developed to help guide therapeutic decision-making.[31] CAC scoring is recommended by both the AHA/ACC/Multisociety and ESC/EAS guidelines to aid risk assessment in those at borderline or intermediate risk under consideration for statin therapy.[3,5] In support of these recommendations, a study of individuals at intermediate risk of ASCVD within MESA demonstrated an association between CAC score and significant improvements in discrimination and risk reclassification for ASCVD events.[32]

The AHA/ACC/Multisociety guidelines recommend initiation of statin therapy for any patient with a CAC score ≥100 Agatston units and/or ≥75th percentile, and statin therapy can be considered for any non-0 score (ie, CAC >0).[3] Recently, a CAC score >300 Agatston units in primary prevention patients has been associated with ASCVD mortality rates equivalent to people with a stable ASCVD secondary prevention-level risk.[33] As such, a CAC score >300 Agatston units may be a suitable threshold at which to treat patients according to the recommended approach for the secondary prevention population (ie, LDL-C reduction ≥50% and target LDL-C <70 mg/dL), who may require the addition of nonstatin lipid-lowering therapy to statins.[34]

Moving Toward Personalized ASCVD Risk Estimation

Current lipid management guidelines acknowledge the limitations of available risk estimation tools, and the recommended application of risk-enhancing factors in borderline or intermediate risk groups within the 2018 AHA/ACC/Multisociety guidelines allows for more personalized risk assessment.[3] Refinement of tools to estimate ASCVD risk remains a focus of research, including on the role of race,[35] sex-specific factors,[36,37] and polygenic risk scores.[38] Incorporation of genetic information may prove beneficial, in particular for individuals at risk of premature ASCVD. For example, the apolipoprotein E ε4 allele, a major genetic risk factor for late-onset Alzheimer disease,[39] is associated with increased LDL-C levels and ASCVD risk.[40,41] Furthermore, genetic predisposition to elevated LDL-C, such as in FH, may decrease efficacy of statins.[42,43]

Nonetheless, in studies comparing risk-enhancing factors, such as ankle-brachial index <0.9, hs-CRP (high-sensitivity C-reactive protein), carotid intima-media thickness, and chronic kidney disease, CAC has shown the best ability for risk reclassification in individuals at intermediate risk of ASCVD events,[44,45] reaffirming the utility of CAC scoring in preventive cardiology practice.

DEFINING THE PROBLEM: LDL-C CONTROL IS NOT SUFFICIENT IN CONTEMPORARY PRACTICE

The Burden of ASCVD

Cardiovascular disease represents the leading cause of death globally and in the United States, and its prevalence is predicted to grow substantially in the coming years.[46–48] In 2020, ≈19 million deaths were attributed to cardiovascular disease worldwide, an increase of 18.7% over 10 years. Of these deaths, >80% were attributable to ASCVD.[47] Morbidity and mortality of cardiovascular disease are associated with significant economic burden, with average annual direct and indirect costs in the United States between 2017 and 2018 estimated as $378 billion.[47]

Elevated LDL-C remains 1 of the top 3 modifiable risk factors contributing to cardiovascular disease burden and represents a significant challenge for health care systems.[46,49] In the United States, the prevalence of elevated LDL-C is high, with an estimated 28% of adults having levels ≥130 mg/dL between 2015 and 2018.[47] Overall prevalence of ASCVD in 2019 in the United States was estimated as 24 million, ≈10% of the total population >21 years of age.[50]

Multiple studies have shown that it is not only the magnitude of LDL-C elevation but also the duration of exposure to elevated LDL-C (or apolipoprotein B lipoproteins), or "LDL-years," that is associated with ASCVD risk.[51–53] Therefore, the timing of the implementation of strategies to decrease lipid levels is key to slowing the progression of atherosclerotic plaques and reducing the risk of ASCVD events.[2] The potential effectiveness of earlier intervention to reduce exposure is supported by the observation that isolated populations who maintain lifetime exposure to low plasma levels of LDL-C have a low lifetime risk of ASCVD.[2,54] Similarly, a meta-analysis of Mendelian randomization studies demonstrated that prolonged exposure to lower LDL-C beginning early in life is associated with a significant reduction in risk of cardiovascular events compared with shorter-term exposure through statin treatment initiated later in life.[55]

Evidence for the Underuse of Lipid-Lowering Therapies in Clinical Practice

Despite guideline recommendations and compelling clinical trial evidence, recent population studies conducted in the United States and Europe have revealed that pharmacotherapy with a primary mechanism of

LDL-C lowering is underused.[9–12,50,56–58] Gu and colleagues reported an increase in the use of lipid-lowering therapies for ASCVD within the United States between 2014 and 2019; however, overall use remained low, with most patients not at guideline-recommended LDL-C thresholds.[50] The persistent underuse of statins in contemporary practice is highlighted by a recently published retrospective study of >600 000 US patients with established ASCVD; during the study period of 2018 to 2019, half of the included patients were not on any statin.[13]

Among patients who receive lipid-lowering therapies, evidence suggests that management of lipid levels remains suboptimal, with many not receiving appropriate treatment intensity or available combination therapies needed to achieve LDL-C goals. A retrospective cohort study of ≈1.5 million patients with a history of ≥1 major ASCVD event reported that >50% of patients meeting the 2018 AHA/ACC/Multisociety guideline very high-risk criteria had LDL-C levels ≥70 mg/dL, despite receiving statins and/or ezetimibe.[58] Similarly, data from the GOULD (Getting to an Improved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia Management) registry showed that over a 2-year period, two-thirds of patients with ASCVD remained with LDL-C levels >70 mg/dL and only 17% received treatment intensification.[9] Recently, an interim report of the European SANTORINI (Treatment of High and Very High Risk Dyslipidemic Patients for the Prevention of Cardiovascular Events in Europe: A Multinational Observational Study) to assess the management of high-risk and very high-risk patients after publication of the ESC/EAS 2019 guidelines showed that combination therapy was used in just 27.3% of patients, of whom 17.1% received statin plus ezetimibe, and 4.1% received an anti-PCSK9 monoclonal antibody plus oral lipid-lowering therapy.[10]

Rates of prescribing of anti-PCSK9 monoclonal antibodies among eligible patients in the United States are low; a 2019 study of electronic health record data from the National Patient-Centered Clinical Research Network reported that <1% of patients with dyslipidemia, LDL-C ≥130 mg/dL, or coronary artery disease or coronary heart disease were prescribed these therapies.[57]

Real-world studies have limitations, including confounding factors, such as selection bias, variability in treatment responses, and adherence (eg, statin avoidance because of concerns around the risk of increased blood glucose and other statin-associated adverse effects, including statin-associated muscle symptoms).[59,60] Nonetheless, these and other published studies provide substantive evidence to support the need for improved LDL-C management in clinical practice to reduce the risk of ASCVD events.

UNDERSTANDING THE BARRIERS TO THE USE OF LIPID-LOWERING THERAPIES

Multiple barriers to the use of lipid-lowering therapy exist, including poor patient adherence and persistence, lack of health care professional familiarity, uncertainty about treatment recommendations (eg, changing guidelines), time constraints and clinical inertia, reimbursement issues, insufficient patient education, adverse effects and concern for risks of adverse effects (both from patients and health care professionals), and polypharmacy.[61–64]

Educational initiatives for patients are one potential solution to some of these barriers. Given the multidisciplinary care received by patients with ASCVD, in addition to physicians, other health care professionals (eg, nurse practitioners, physician assistants, and clinical pharmacists) provide important education to patients on the adverse effects of long-term elevated LDL-C, the benefits of lifestyle modification, and the role of lipid-lowering therapies.[3,65,66] Initiatives should also target clinicians, raising awareness of guideline recommendations for ASCVD management and the need for monitoring of LDL-C levels to inform on efficacy of therapy or the requirement for treatment intensification.[67] Interventions, such as personalized electronic reminders of a patient's diagnosis, medications, and including links to guideline resources, may assist with overcoming clinical inertia.[68] To address adherence and concerns of adverse effects from therapies, shared decision-making should be implemented in clinical practice and is recommended in lipid management guidelines.[3,6,69] As most patients with ASCVD have other chronic conditions, the ACC has recently published an ECDP for integrating evidence-based therapies into personalized approaches for patients.[70]

For monoclonal antibodies targeting PCSK9, high cost and a complex preauthorization process have been linked to significant underuse, particularly following initial US Food and Drug Administration approval.[57,71] Since 2018, the costs of these antibodies in the United States have decreased, and prior authorization checklists have since been developed, such as the resources available from the National Lipid Association and the American Society for Preventive Cardiology.[72,73]

Cost and complex preauthorization processes are also likely to present barriers to access to newer lipid-lowering therapies. A recent publication detailing early clinical experience with inclisiran in a US lipid clinic suggests that younger patients with non-Medicare insurance may face challenges in accessing therapy.[74] Similarly, real-world use of bempedoic acid is reportedly hampered by insurance and cost barriers.[75]

Cost-effectiveness studies and the development of resources, such as prior authorization checklists, may assist in overcoming these barriers for some patients.[76,77] Clinicians can also direct patients to applicable assistance programs to assist with financial barriers.[78]

Are Low Levels of LDL-C Harmful?

Observational studies have raised questions about the safety of low levels of LDL-C achieved through intensive lipid lowering;[79] however, there does not appear to be a "too low" level of LDL-C. Populations with naturally occurring low levels of LDL-C exist, and studies of individuals with genetic mutations leading to reduced LDL-C levels reveal no safety issues and have shown an association with reduced ASCVD risk.[80,81] This notion is recognized by the lower LDL-C goals in the 2019 ESC/EAS guideline, which recommend target LDL-C levels as low as <55 and <40 mg/dL, the latter for patients who have had multiple ASCVD events within 2 years.[5]

Achievement of very low LDL-C levels in clinical trials of lipid-lowering therapies has not been associated with an increased prevalence of adverse events.[82–86] In the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial of evolocumab added to statin therapy, 42% of patients achieved LDL-C levels ≤25 mg/dL at 48 weeks with no significant difference between the evolocumab and placebo groups in terms of adverse events beyond injection-site reactions.[82] In a prespecified analysis of IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), patients who achieved very low LDL-C levels (<30 mg/dL) at 1 month after acute coronary syndrome had a similar safety profile over a period of 6 years compared with patients who achieved LDL-C concentrations ≥30 mg/dL; furthermore, the very low LDL-C group had the numerically lowest rate of cardiovascular events.[84] In addition, the EBBINGHAUS (Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects) trial of patients who received evolocumab or placebo added to statins showed no significant between-group difference in cognitive function, even among patients who achieved very low levels of LDL-C (<25 mg/dL).[87]

Although some epidemiological studies have reported an association between low LDL-C levels and hemorrhagic stroke,[88,89] it is noteworthy that these studies may be subject to residual confounding factors. Individuals with very low LDL-C may have poorer health status than their counterparts with higher LDL-C levels (eg, attributable to comorbidities, cancer, liver disease, alcoholism, and frailty, and not as a result of lipid-lowering therapies). Thus, these findings may represent associations without causality.[90] Moreover, in the FOURIER and ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trials, there were no significant differences in the occurrence of hemorrhagic stroke between groups treated with anti-PCSK9 monoclonal antibodies and placebo.[82,91]

How Do we Identify Patients Who Are Undertreated?

There is an unmet need for improved identification of patients with elevated LDL-C who remain undertreated, particularly those at very high risk of events.[92] In addition to educational efforts to raise awareness among patients and health care professionals, the application of system tools based on electronic health care records may be of value. One such example is the Systematic Lab Knowledge Integration for Management of Lipid Excess in High-Risk Patients project in Italy, developed to aid the identification and early referral of patients with hypercholesterolemia who may be inadequately controlled.[93] In the United States, a remote cholesterol management program led by navigators and pharmacists and supported by cardiovascular clinicians, achieved a mean reduction in LDL-C of 37.5 mg/dL at 12 months in patients enrolled in the lipid program, compared with a mean reduction in LDL-C of 10.2 mg/dL in patients who received education alone (P<0.001).[94] A study of personalized electronic reminders sent to primary care physicians, mostly 2 to 7 days before patient visits, led to a significant increase in high-intensity statin use; however, 31.6% of clinicians opted out from the electronic reminders over the course of the study.[68] The ongoing PROMPT (Pragmatic Trial of Messaging to Providers About Treatment of Hyperlipidemia) study is also evaluating the effectiveness of a real-time, targeted electronic health care record alert to promote intensification of evidence-based lipid-lowering therapy and reduction of LDL-C in patients with very high-risk ASCVD.[95]

HOW AND WHEN TO USE AVAILABLE PHARMACOLOGIC TOOLS FOR LDL-C LOWERING

On top of a healthy diet and lifestyle change, many pharmacologic tools are at our disposal to help lower the LDL-C–mediated risk for ASCVD. In addition to statins, several nonstatin lipid-lowering therapies are now available; through direct or indirect mechanisms, these share a final "common pathway" of increased expression of the LDL receptor on hepatocytes. Herein, we describe the key evidence supporting the utility of these tools for the management of LDL-C levels in individuals at risk of ASCVD; the properties of these

Table 2. Pharmacological Tools to Help Lower LDL-C–Mediated Risk for ASCVD

Drug	Mechanism of action	Administration	Dosing frequency	LDL-C reduction	Action on other lipids/ biomarkers	Common adverse reactions
Statins[3,96]	Inhibition of HMG-CoA reductase	Oral	Daily	High intensity: ≥50% Moderate intensity: 30%–49% Low intensity: <30%	Modest HDL-C increase, reduce triglycerides	Muscle toxicity (myalgia, myopathy, myositis, rhabdomyolysis), mild transaminase elevation with rare risk for liver toxicity, elevated blood glucose with risk for new-onset diabetes
Bile acid sequestrants[3,6]	Inhibit intestinal absorption of bile acids	Oral	Daily or twice a day	+Statins: 15%–30%	Can cause severe hypertriglyceridemia*	Gastrointestinal adverse effects; contraindicated in patients with hypertriglyceridemia
Ezetimibe[3,97,98]	Cholesterol absorption inhibitor	Oral†,‡	10 mg daily	Monotherapy: 13%–20% +Statins: 13%–20%	Reduces triglycerides, increases HDL-C	Arthralgia, diarrhea, URTI
Alirocumab[99–101]	Humanized monoclonal antibody against PCSK9	Subcutaneous	75–150 mg Q2W or 300 mg Q4W	Monotherapy: ≈60% +Statins: ≈60%	Reduces lipoprotein(a) and triglycerides	Injection-site reactions, nasopharyngitis, influenza
Evolocumab[3,82,102,103]	Humanized monoclonal antibody against PCSK9	Subcutaneous	140 mg Q2W or 420 mg Q4W	Monotherapy: ≈60% +Statins: ≈60%	Reduces lipoprotein(a) and triglycerides	Injection-site reactions, diabetes, nasopharyngitis, URTI, influenza, back pain
Bempedoic acid[7,104–107,113]	ACL inhibitor	Oral‡	180 mg daily	Monotherapy: ≈24% +Statins: ≈17% FDC‡+statins: 36%	Slight reduction in HDL-C, significant reduction in hs-CRP	Hyperuricemia, gout, cholelithiasis, URTI, muscle spasms, back pain, abdominal pain, pain in extremity, bronchitis, anemia, elevated liver enzymes
Evinacumab[108,109]	Humanized monoclonal antibody against ANGPTL3	Intravenous	15 mg/kg Q4W	+Statins: 47% (currently only approved for HoFH)	Reduces triglycerides	Flu-like symptoms, nasopharyngitis, dizziness, rhinorrhea, nausea
Inclisiran[8,110]	siRNA PCSK9 inhibitor	Subcutaneous	300 mg Q6M§	+Statins: time-averaged ≈50%	Reduces lipoprotein(a) and triglycerides, increases HDL-C	Injection-site reactions, arthralgia, UTI, diarrhea, bronchitis, pain in extremity, dyspnea

ACL indicates ATP-citrate lyase; ANGPTL3, angiopoietin-like 3; ASCVD, atherosclerotic cardiovascular disease; FDC, fixed-dose combination; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia, hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; Q6M, every 6 months; Q2W, every 2 weeks; Q4W, every 4 weeks; siRNA, small interfering RNA; URTI, upper respiratory tract infection; and UTI, urinary tract infection.

*In patients with fasting triglycerides ≥300 mg/dL.

†A fixed-dose rosuvastatin plus ezetimibe formulation is available.[127]

‡A fixed-dose bempedoic acid plus ezetimibe formulation is available.[119]

§After an initial dose and a dose at 3 months (300 mg inclisiran sodium is equivalent to 284 mg of the free acid form).

agents are summarized in Table 2.[3,6–8,82,96–110] Although beyond the scope of this review, lipoprotein apheresis, under the care of a lipid specialist, is a treatment option in patients with severe hypercholesterolemia (heterozygous FH [HeFH] or homozygous FH) who have an inadequate response to pharmacologic therapy.[3,6]

As bempedoic acid and inclisiran represent the newest tools for LDL-C lowering in ASCVD, further details of their clinical studies are included in Table 3[104,106,111–113] and Table 4,[110,114–118] respectively, with practical points for their use summarized in Figure 3.[7,8,107,110,113,117–119]

Statins

Lipid lowering with statin therapy has been the cornerstone of the prevention and treatment of ASCVD over the past 3 decades. High-intensity statins can reduce LDL-C levels by ≥50%, which has been shown to reduce the risk of major ASCVD events significantly.[3–5] Magnitude of LDL-C lowering directly relates to efficacy; however, a meta-analysis of randomized controlled trials and data from JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) confirm wide variation in the degree of LDL-C reduction achieved among individuals treated with statins.[120,121]

In terms of safety, statins are generally well tolerated, but statin-associated adverse effects occur in some patients. Most frequent are statin-associated muscle symptoms, reported to affect between 1 in 1000 and 1 in 10 000 people treated with standard doses.[122] Statin-associated muscle symptoms, or fear of statin-associated muscle symptoms, are key factors leading to statin discontinuation or nonadherence, which remain challenging in clinical practice and contribute to adverse ASCVD outcomes.[3,122,123] Statins can also cause adverse effects on glucose homeostasis and modestly increase the risk of new-onset diabetes in individuals with predisposing risk factors, including those with prediabetes.[3,5] This does not detract from recommendations to use statins in this population, given the associated reduction in ASCVD risk.

Ezetimibe

Ezetimibe targets the Niemann-Pick C1-like 1 protein, reducing cholesterol absorption from the intestine.[97] Clinical studies have shown that ezetimibe in combination with statins is well tolerated and significantly reduces LDL-C levels by up to an additional 24% compared with statins alone.[83,124,125] More importantly, in the IMPROVE-IT trial of patients with a recent hospitalization for acute coronary syndrome and LDL-C ≤125 mg/dL (mean baseline LDL-C ≈94 mg/dL), the addition of ezetimibe to simvastatin significantly reduced LDL-C levels (53.7 versus 69.5 mg/dL; $P<0.001$) and rate of recurrent cardiovascular events (32.7% versus 34.7%; $P=0.016$; number needed to treat=50) compared with simvastatin alone.[83] There is less evidence for the use of ezetimibe in primary prevention; however, an open-label trial in adults ≥75 years of age in Japan showed that treatment with ezetimibe, in addition to dietary counseling, led to a significant reduction in the incidence of cardiovascular events compared with dietary counseling alone (hazard ratio [HR], 0.66 [95% CI, 0.50–0.86]; $P=0.002$).[126]

The ACC/AHA/Multisociety and ESC/EAS guidelines recommend the addition of ezetimibe to maximally tolerated statin therapy for patients at very high risk of ASCVD events with LDL-C levels above targets (≥70 and ≥55 mg/dL, respectively).[3,5] A fixed-dose rosuvastatin plus ezetimibe formulation is available, which may improve medication adherence.[127]

Anti-PCSK9 Monoclonal Antibodies

Monoclonal antibodies that target PCSK9 (alirocumab and evolocumab) have been shown to reduce LDL-C levels by ≈60% when added to statin therapy, with few adverse events.[128] In cardiovascular outcome trials of patients at very high risk for ASCVD, anti-PCSK9 antibodies have been shown to significantly reduce the risk of major adverse cardiovascular events (MACE).

In the FOURIER trial of patients with clinical ASCVD and LDL-C ≥70 mg/dL, evolocumab added to background statin therapy (with or without ezetimibe) lowered LDL-C levels to a median of 30 mg/dL at 48 weeks and reduced the risk of MACE by 15% versus statins plus placebo (HR, 0.85 [95% CI, 0.79–0.92]).[82] Clinical benefit was demonstrated across baseline LDL-C subgroups, and the magnitude of risk reduction for the primary and secondary end points increased over time. Furthermore, evolocumab conferred even greater absolute and relative risk reduction among higher-risk patients, such as those with recent myocardial infarction, more extensive coronary artery disease, or peripheral arterial disease.[129,130] In addition, during the open-label extension follow-up period of the FOURIER trial, patients who were originally randomized to evolocumab had a 15% to 20% lower risk of MACE and a 23% lower risk of cardiovascular death than those randomized to placebo.[131] Similarly, in the ODYSSEY Outcomes trial of patients with recent acute coronary syndrome and LDL-C ≥70 mg/dL, the addition of alirocumab to maximally tolerated statins reduced the risk of cardiovascular events by 15% versus placebo (HR, 0.85 [95% CI, 0.78–0.93]; $P<0.001$) after a median follow-up of 2.8 years.[99]

In addition to lowering LDL-C, anti-PCSK9 monoclonal antibodies have been shown to reduce plasma lipoprotein(a) by up to ≈25%.[128] In the FOURIER trial, evolocumab significantly reduced lipoprotein(a) levels by a median of 26.9% (interquartile range, 6.2%–46.7%),

Table 3. Clinical Trials of Bempedoic Acid

Clinical trial	Population	Treatment arms	Duration	Change from baseline in LDL-C	Change from baseline in additional outcomes	Safety
CLEAR Harmony phase 3 trial (N=2230)[104]	ASCVD, HeFH, or both, and taking maximally tolerated statin therapy with a fasting LDL-C ≥70 mg/dL	BA 180 mg daily (n=1488) Placebo (n=742)	52 wk	At week 12: BA=−16.5% Placebo=1.6%	hs-CRP: BA=−14.4% Placebo=1.8%	Incidence of gout: BA=1.2% Placebo=0.3% SAE incidence: BA=14.5% Placebo=14.0% % Patients discontinuing because of an AE: BA=10.9% Placebo=7.1%
CLEAR Tranquility phase 3 trial (N=269)[111]	History of statin intolerance and LDL-C ≥100 mg/dL while on stable lipid-modifying therapy	BA 180 mg daily+ezetimibe 10 mg/d (n=181) Placebo+ezetimibe 10 mg/d (n=88)	12 wk	At week 12: BA=−23.5% Placebo=5.0%	hs-CRP: BA=−32.5% Placebo=2.1%	Serious TEAE incidence: BA=2.8% Placebo=3.4% % Patients discontinuing because of a TEAE: BA=6.1% Placebo=5.7%
CLEAR Wisdom phase 3 trial (N=779)[112]	At high risk of ASCVD, HeFH, or both, and with LDL-C ≥100 mg/dL at screening while on stable, maximally tolerated lipid-lowering therapy	BA 180 mg daily (n=522) Placebo (n=257)	52 wk	At week 12: BA=−15.1% Placebo=2.4%	hs-CRP: BA=−16.7% Placebo=−6.3%	Gout: BA=2.1% Placebo=0.8% SAE incidence: BA=20.3% Placebo=18.7% % Patients discontinuing because of an AE: BA=10.9% Placebo=8.6%
CLEAR Serenity phase 3 trial (N=345)[106]	Hypercholesterolemia and a history of intolerance to ≥2 statins	BA 180 mg daily (n=234) Placebo (n=111)	24 wk	At week 12: BA=−23.6% Placebo=−1.3%	hs-CRP: BA=−25.1% Placebo=4.4%	Gout: BA=1.7% Placebo=0.9% SAE incidence: BA=6.0% Placebo=3.6% % Patients discontinuing because of an AE: BA=18.4% Placebo=11.7%
CLEAR Outcomes[113] (N=13 970)	Established ASCVD or high risk of developing ASCVD; documented statin intolerance; LDL-C ≥100 mg/dL while on maximally tolerated lipid-lowering therapy	BA 180 mg daily Placebo	Median 40.6 mo	At 6 mo: BA=−21.7% Placebo=−0.6%	hs-CRP: BA=−22.2% Placebo=2.4% Incidence of 4-point MACE: BA=11.7% Placebo=13.3%	Gout: BA=3.1% Placebo=2.1% SAE incidence: BA=25.2% Placebo=24.9% % Patients discontinuing because of an AE: BA=10.8% Placebo=10.4%

AE indicates adverse event; ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; CLEAR, Cholesterol Lowering via Bempedoic Acid, an ACL [ATP-Citrate Lyase]-Inhibiting Regimen; HeFH, heterozygous familial hypercholesterolemia; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; SAE, serious AE; and TEAE, treatment-emergent AE.

Table 4. Clinical Trials of Inclisiran

Clinical trial	Population	Treatment arms	Duration	Change from baseline in LDL-C	Change from baseline in additional outcomes	Safety
ORION-6 phase 1 trial (N=28)[114]	Patients with mild (n=10) or moderate HI (n=6) and patients with normal HF (n=12)	Single-dose regimen: 300 mg inclisiran subcutaneous	60 d	At day 60: Normal HF=−51.9% Mild HI=−53.2% Moderate HI=−39.7%		Injection-site pain: Normal HF=0.0% Mild HI=20.0% Moderate HI=0.0% SAE incidence: Normal HF=0.0% Mild HI=0.0% Moderate HI=16.7%
ORION-1 phase 2 trial (N=501)[115]	LDL-C ≥70 mg/dL (history of ASCVD) or LDL-C ≥100 mg/dL (no history of ASCVD)	Single-dose regimen (subcutaneous): 200 mg inclisiran (n=60) 300 mg inclisiran (n=61) 500mg inclisiran (n=65) Placebo (n=65) Two-dose regimen (subcutaneous)†: 100 mg inclisiran (n=61) 200 mg inclisiran (n=62) 300 mg inclisiran (n=61) Placebo (n=62)	180 d	At day 180: Single-dose regimen: 200 mg=−27.9% 300 mg=−38.4% 500 mg=−41.9% Placebo=2.1% Two-dose regimen*: 100 mg=−35.5% 200 mg=−44.9% 300 mg=−52.6% Placebo=1.8%	hs-CRP, single-dose regimen: 200 mg=7.1% 300 mg=−16.2% 500 mg=−19.8% Placebo=−5.3% hs-CRP, 2-dose regimen*: 100 mg=−12.5% 200 mg=−16.3% 300 mg=−16.7% Placebo=−20.0%	Injection-site reactions: Inclisiran=5.1% Placebo=0.0% SAE incidence: Inclisiran=11% Placebo=8% % Patients discontinuing because of an AE: Inclisiran=0.2% Placebo=0.8%
ORION-9 phase 3 trial (N=482)[116]	HeFH and LDL-C ≥100 mg/dL despite receiving the maximally accepted dose of statin therapy with or without ezetimibe	Four-dose regimen (subcutaneous)‡: 300 mg inclisiran (n=242) Placebo (n=240)	540 d	At day 510: Inclisiran=−39.7% Placebo=8.2%	hs-CRP (median)†: Inclisiran=0% Placebo=4.0% Lipoprotein(a) (median)†: Inclisiran=−13.5% Placebo=3.7%	Injection-site reactions: Inclisiran=17.0% Placebo=1.7% SAE incidence: Inclisiran=7.5% Placebo=13.8% % Patients discontinuing because of an AE: Inclisiran=1.2% Placebo=0%
ORION-10 phase 3 trial (N=1561)[110]	ASCVD and LDL-C ≥70 mg/dL despite receiving the maximally accepted dose of statin therapy with or without ezetimibe	Four-dose regimen (subcutaneous)‡: 300 mg inclisiran (n=781) Placebo (n=780)	540 d	At day 510: Inclisiran=−51.3% Placebo=1.0%	hs-CRP (median)†: Inclisiran=0% Placebo=−8.8% Lipoprotein(a) (median)†: Inclisiran=−21.9% Placebo=3.7%	Injection-site reactions: Inclisiran=2.6% Placebo=0.9% SAE incidence: Inclisiran=22.4% Placebo=26.3% % Patients discontinuing because of an AE: Inclisiran=2.4% Placebo=2.2%

(*Continued*)

Table 4. Continued

Clinical trial	Population	Treatment arms	Duration	Change from baseline in LDL-C	Change from baseline in additional outcomes	Safety
ORION-11 phase 3 trial (N=1617)[110]	ASCVD and LDL-C ≥70 mg/dL or an ASCVD risk equivalent[§] and LDL-C ≥100 mg/dL	Four-dose regimen (subcutaneous)[‡]: 300 mg inclisiran (n=810) Placebo (n=807)	540 d	At day 510: Inclisiran=−45.8% Placebo=4.0%	hs-CRP (median)[†]: Inclisiran=0% Placebo=−8.9% Lipoprotein(a) (median)[†]: Inclisiran=−18.6% Placebo=0%	Injection-site reactions: Inclisiran=4.7% Placebo=0.5% SAE incidence: Inclisiran=22.3% Placebo=22.5% % Patients discontinuing because of an AE: Inclisiran=2.8% Placebo=2.2%
ORION-4 (estimated N=15 000)[117]	History of MI or ischemic stroke or PAD	300 mg inclisiran subcutaneous[‖] Placebo	5 y	…	…	…
VICTORION-2 PREVENT[118] (estimated N=15 000)	Established cardiovascular disease[#], LDL-C ≥70 mg/dL and on stable lipid-lowering therapy	300 mg inclisiran subcutaneous[‖] Placebo	Up to 72 mo	…	…	…

AE indicates adverse event; ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; HF, hepatic function; HI, hepatic impairment; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral arterial disease; and SAE, serious AE.

*Days 1 and 90.

†Day 540 sampling point.

‡Days 1, 90, 270, and 450.

§Type 2 diabetes, HeFH, or a 10-year risk of a cardiovascular event of ≥20%.

‖Days 1 and 90 followed by every 180 days.

#Defined as any of the following: spontaneous myocardial infarction ≥4 weeks from screening visit, history of ischemic stroke ≥4 weeks before the screening visit, symptomatic PAD evidenced by intermittent claudication with ankle-brachial index <0.85, prior peripheral arterial revascularization procedure, or amputation attributable to atherosclerotic disease.

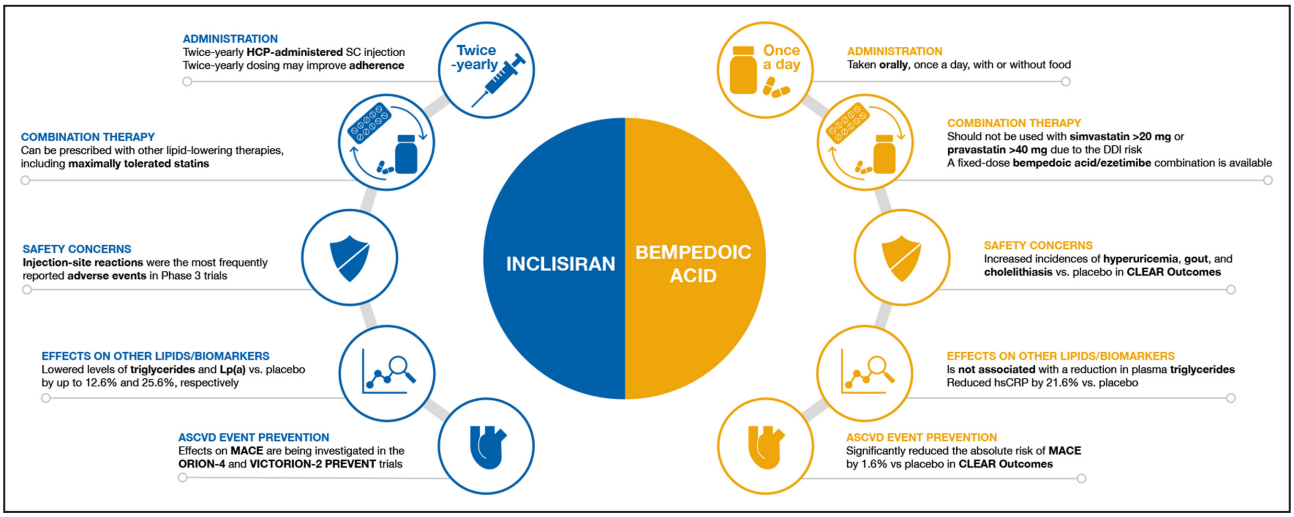

Figure 3. Practical points: bempedoic acid and inclisiran.[7,8,107,110,113,117–119]
ASCVD indicates atherosclerotic cardiovascular disease; CLEAR, Cholesterol Lowering via Bempedoic Acid, an ACL [ATP-Citrate Lyase]-Inhibiting Regimen; DDI, drug––drug interaction; HCP, health care professional; hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein(a); MACE, major adverse cardiovascular events; and SC, subcutaneous.

and in patients with higher baseline lipoprotein(a) levels, it reduced the risk of cardiovascular events by 23% versus placebo (HR, 0.77 [95% CI, 0.67–0.88]), which was greater than the reduction in events among individuals with lower levels of lipoprotein(a).[132] Lipoprotein(a) lowering by alirocumab in the ODYSSEY Outcomes trial independently predicted a lower risk of cardiovascular events, suggesting that lipoprotein(a) may represent an independent treatment target in ASCVD.[133] Importantly, these clinical trials were not enriched for patients with elevated lipoprotein(a); therefore, the absolute reductions observed in lipoprotein(a) levels were fairly modest.

Both the ACC/AHA/Multisociety and ESC/EAS guidelines recommend the addition of evolocumab or alirocumab to statins and ezetimibe in patients at very high risk of ASCVD events who remain above LDL-C thresholds (≥70 and ≥55 mg/dL, respectively), as well as in primary prevention patients with FH who remain above an LDL-C threshold of ≥100 mg/dL.[3,5]

Bempedoic Acid

Bempedoic acid is an oral, once-daily, hypolipidemic prodrug that targets cholesterol synthesis in the liver by inhibiting ATP-citrate lyase. As bempedoic acid is not activated in skeletal muscle, it is thought to have a lower potential for myotoxic effects than statins.[134] In early 2020, bempedoic acid received US Food and Drug Administration approval as an adjunct treatment to maximally tolerated statins, and a fixed-dose combination of bempedoic acid and ezetimibe is recommended for the treatment of HeFH or established ASCVD.[134] Practical points on the use of bempedoic acid are summarized in Figure 3.

In the CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL [ATP-Citrate Lyase]-Inhibiting Regimen) Harmony trial of patients with ASCVD, HeFH, or both, bempedoic acid added to statin therapy reduced LDL-C levels by 18.1% (95% CI, 16.1%–20.0%; $P<0.001$) versus placebo.[104] Incidence of adverse events, including muscle related, was similar between treatment arms, except for gout, which was increased in patients receiving bempedoic acid (1.2% versus 0.3%; $P=0.03$). In patients at high risk of ASCVD on background statin therapy, the bempedoic acid and ezetimibe fixed-dose combination added to background statin therapy significantly reduced LDL-C by 38% (95% CI, 29.6%–46.5%; $P<0.001$) compared with placebo.[105] The fixed-dose combination also significantly lowered LDL-C levels versus bempedoic acid and ezetimibe monotherapies. Recently, the CLEAR Outcomes study reported significantly decreased incidence of MACE in patients with statin intolerance (including 30% without a history of established ASCVD) treated with bempedoic acid compared with placebo (11.7% versus 13.3%; HR, 0.87 [95% CI, 0.79–0.96]; $P=0.004$).[113] At 6 months, compared with placebo, bempedoic acid reduced LDL-C by 29.2 mg/dL or 21.1% (95% CI, 20.3%–21.9%). The study enrolled 48% women, for whom the HR for the primary end point was similar to that for men. Clinical studies of bempedoic acid are summarized in Table 2.

Unlike PCSK9-inhibiting monoclonal antibodies, bempedoic acid has shown anti-inflammatory effects. In the CLEAR Outcomes study, compared with placebo, bempedoic acid was associated with a 21.6% (95% CI, 19.6%–23.7%) reduction in hs-CRP,[113] an ASCVD risk enhancer in the 2018 ACC/AHA/Multisociety guidelines.[3] Furthermore, bempedoic acid

was not associated with increased incidence of new-onset or worsening diabetes.[113]

The recent 2022 ACC ECDP on the role of nonstatin therapies in ASCVD recommends consideration of bempedoic acid in patients with ASCVD at very high risk who require further LDL-C lowering (ie, who have achieved <50% reduction in LDL-C or LDL-C remains ≥55 mg/dL) despite receiving maximally tolerated statins, ezetimibe, or an anti-PCSK9 monoclonal antibody.[6]

Inclisiran

Inclisiran is a first-in-class small interfering RNA that uses RNA interference to degrade PCSK9 mRNA, reducing the hepatic synthesis of PCSK9 protein and thereby increasing hepatic LDL receptor expression. It is administered by a health care professional, twice yearly, as a subcutaneous injection, following initial doses at baseline and 3 months.[110] Inclisiran received US Food and Drug Administration approval in December 2021 for the treatment of HeFH or ASCVD as an adjunct to maximally tolerated statins.[6,8] Practical points on the use of inclisiran are summarized in Figure 3.

The magnitude of LDL-C lowering with inclisiran is ≈50%, slightly less than the levels achieved with anti-PCSK9 monoclonal antibodies and greater than for bempedoic acid as monotherapy and in combination with ezetimibe. A pooled analysis of phase 3 studies of inclisiran involving patients with HeFH (ORION-9 trial) or ASCVD and ASCVD risk equivalents (ORION-10 and ORION-11 trials) receiving maximally tolerated statins, with or without ezetimibe, showed that inclisiran reduced LDL-C levels by 50.7% (95% CI, 48.4%–52.9%; $P<0.0001$) versus placebo.[135] Similar to the anti-PCSK9 monoclonal antibodies, in addition to reducing LDL-C, inclisiran was shown to modestly lower lipoprotein(a) and triglyceride levels (median reductions of 19.5% and 13.3%, respectively). LDL-C lowering was shown to be consistent across a range of statin doses, and safety was similar between treatment groups, although treatment-emergent events at the injection site were more frequent with inclisiran than with placebo (5.0% versus 0.7%; risk ratio, 7.54 [95% CI, 4.14–13.71]). Other clinical studies have shown that inclisiran is well tolerated; analyses of patients with kidney impairment from the ORION-1 and ORION-7 trials concluded that dose adjustment of inclisiran is not required in this population.[136] Moreover, the ORION-6 trial reported that inclisiran was well tolerated in patients with mild or moderate hepatic impairment, although patient numbers were low.[114] Clinical studies of inclisiran are summarized in Table 3.

Analysis of a prespecified exploratory cardiovascular composite end point (comprising a Medical Dictionary for Regulatory Activities–defined cardiovascular basket of nonadjudicated terms) in the ORION-10 and ORION-11 trials reported lower frequency in the inclisiran group versus placebo.[110] Although these preliminary observations are based on a low number of adverse events, they are consistent with the general concept that lowering LDL-C reduces the risk of future cardiovascular events. These data support the current research in the phase 3 ORION-4 and VICTORION-2 PREVENT CV outcome trials.[137]

The recent 2022 ACC ECDP on the role of nonstatin therapies in ASCVD emphasizes the need to intensify lipid-lowering therapy in patients with elevated LDL-C in the secondary prevention setting.[6] Addition of nonstatin lipid-lowering therapies is recommended in patients who require additional LDL-C lowering with differing target thresholds based on the patient's level of risk. The current role of inclisiran as a nonstatin lipid-lowering therapy is included in the ECDP, and recommendations consider both the LDL-C–lowering efficacy of inclisiran and ongoing clinical trials to evaluate the ability of inclisiran to reduce cardiovascular events.

LOOKING TO THE FUTURE: MANY TREATMENT OPTIONS, MANY OPPORTUNITIES TO REDUCE ASCVD RISK

Investigational Lipid-Lowering Therapies

The safety and efficacy of lipid-lowering therapies continue to improve as more targeted therapies are developed. PCSK9 inhibition has been demonstrated as an effective strategy for LDL-C lowering, and several new targeted therapies are currently in clinical development. An oral PCSK9 inhibitor, MK-0616 (a macrocyclic peptide), demonstrated significant, placebo-adjusted reductions in LDL-C of up to 60.9% at week 8 in a phase 2b study.[138] Lerodalcibep, a novel recombinant fusion protein of the PCSK9-binding domain and human serum albumin, has been shown to lower LDL-C levels by ≈60% in a phase 2 extension study.[139]

Several studies have examined LDL-C lowering following CETP (cholesteryl ester transfer protein) inhibition; however, to date, CETP inhibitors have failed to reduce ASCVD events in late-stage clinical trials with some safety concerns. Obicetrapib, a new-generation CETP inhibitor, has achieved significant reductions of LDL-C by 50.8% and is currently under phase 3 development.[140]

Among novel therapeutic targets for LDL-C reduction is angiopoietin-like 3, an inhibitor of lipoprotein lipase and endothelial lipase. Evinacumab, an anti–angiopoietin-like 3 monoclonal antibody indicated for the treatment of patients with homozygous FH, reduced LDL-C levels by >50% in a phase 2 study of patients with refractory hypercholesterolemia.[141] However, in

the TRANSLATE-TIMI 70 (Targeting ANGPTL3 With an Antisense Oligonucleotide in Adults With Dyslipidemia) trial of patients on statin therapy, vupanorsen, an antisense oligonucleotide targeting angiopoietin-like 3, demonstrated only modest LDL-C lowering of between 7.9% and 16.0%.[142] Vupanorsen was also associated with a dose-dependent increase in hepatic fat and more frequent elevations of liver enzymes compared with placebo; therefore, further clinical development of this drug has been halted.

Redefining ASCVD: The Role of Lipid-Lowering Therapies on Atherosclerotic Plaque

How we define ASCVD is changing; although a reduction in MACE is a critical end point, future research should examine the potential mechanisms by which lipid-lowering therapies reduce the risk for ASCVD with attention to the entire risk continuum, including subclinical atherosclerosis.

One key question to be addressed is whether lipid-lowering therapies differ on their effects on plaque composition and formation or if a class effect of LDL-C lowering exists. Data support that beneficial changes in atherosclerotic plaque occur with statins, including slower plaque progression, evidence of regression, and favorable remodeling from lipid-rich to more dense, calcified plaque.[143,144] Similarly, PACMAN-AMI (Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction) study and HUYGENS (High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study) have shown evidence of the positive effects of anti-PCSK9 monoclonal antibodies on plaque stabilization and regression.[145,146] Although not mediated by LDL-C lowering, icosapent ethyl has also been studied for its effects on atherosclerotic plaque, with favorable outcomes observed in the EVAPORATE (Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy) trial.[147]

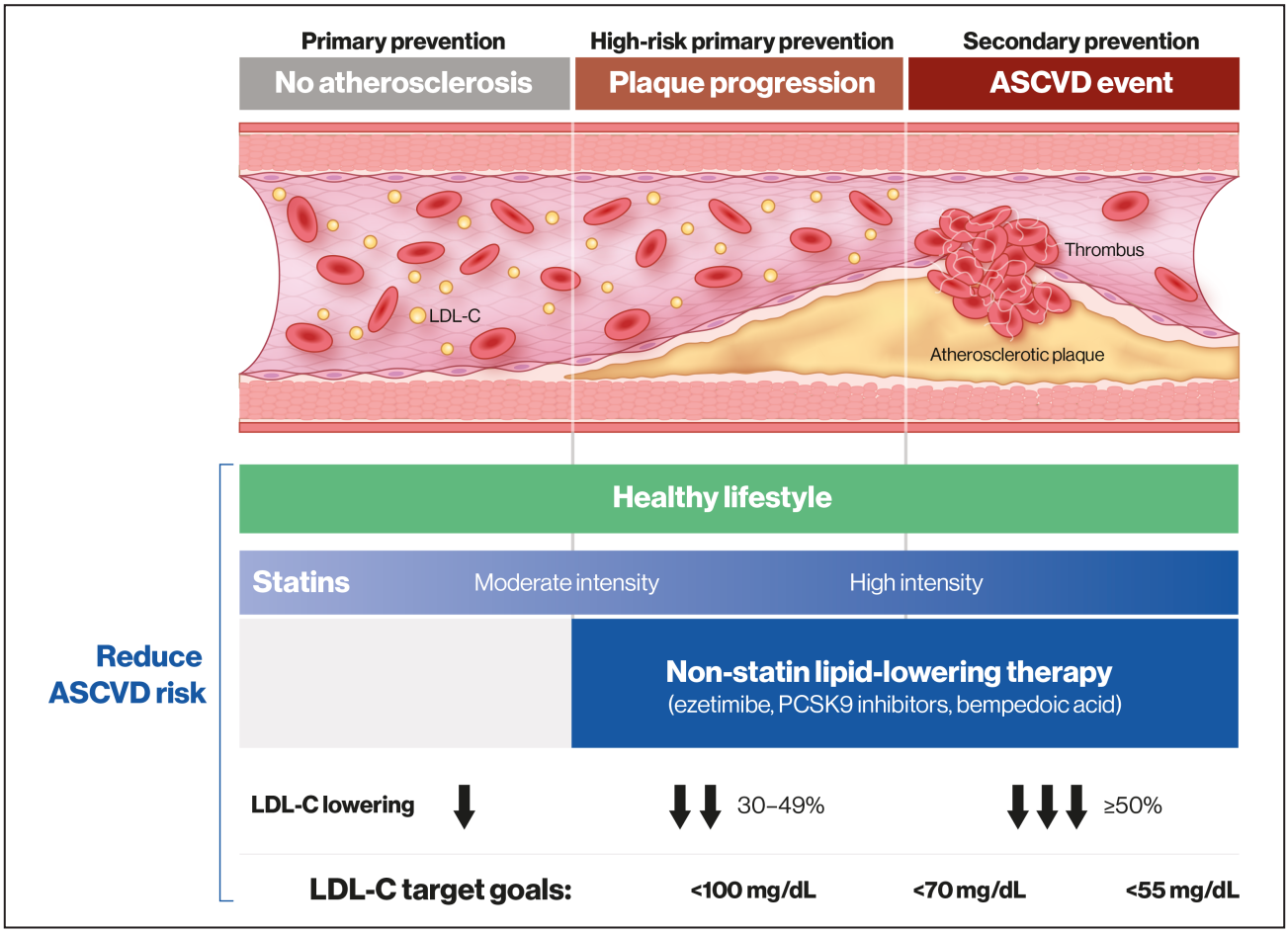

Figure 4. The continuum of atherosclerotic cardiovascular disease (ASCVD) risk.
Management of low-density lipoprotein cholesterol (LDL-C) levels across the continuum of ASCVD risk to prevent first and subsequent cardiovascular events. PCSK9 indicates proprotein convertase subtilisin/kexin type 9.

Therefore, in addition to measuring the effects of emerging lipid-lowering therapies on rates of cardiovascular events, clinical trial end points should focus on the pathologic mechanisms of ASCVD, assessing changes in existing plaque composition and effects on plaque progression or regression. Evidence that lipid-lowering therapies contribute to favorable changes in atherosclerotic plaque could provide further justification for their use in patients at an earlier point along the continuum of ASCVD risk and atherosclerosis progression.

Addressing the Continuum of ASCVD Risk

To fully realize the potential of available and future LDL-C–lowering therapies, we propose an approach of earlier identification and more aggressive treatment of individuals at the highest risk of ASCVD events. LDL-C management should consider each patient's risk across the continuum of ASCVD, including subclinical atherosclerosis, the degree of desired LDL-C lowering, the role of pharmacotherapy, and LDL-C targets or thresholds (Figure 4). Although statins form the backbone of therapy, achieving a >50% reduction in LDL-C levels with high-intensity statins is often insufficient for patients at the highest risk of ASCVD events; thus, it is key to identify high-risk patients for whom a statin is only the beginning of a multidrug regimen to lower their ASCVD risk aggressively. For patients at very high risk who require LDL-C lowering of ≥50%, there should be a consideration for early, upfront combination lipid-lowering therapy and therapy titration every 4 to 12 weeks until LDL-C goals are achieved.[61,62] Use of fixed-dose formulations may circumvent some of the barriers associated with LDL-C lowering, such as medication adherence and polypharmacy.

Non–LDL-C targets, such as lipoprotein(a) and triglycerides, pose a residual risk of ASCVD and should also be addressed. Emerging therapies targeting lipoprotein(a) include small interfering RNAs, olpasiran and SLN360, and an antisense oligonucleotide, pelacarsen, which has also been reported to reduce lipoprotein(a) by up to 80% while modestly reducing LDL-C in phase 2 studies[27,148] Evinacumab and the antisense oligonucleotide, olezarsen (IONIS-APOCIII-LRx), are being investigated for the reduction of triglyceride-rich lipoproteins.[149] However, a comprehensive discussion of these novel agents is beyond the scope of this review.

CONCLUSIONS

In summary, a personalized approach, identifying patients at risk of ASCVD earlier in the risk continuum and optimizing the use of available lipid-lowering therapies in combination with statins, will enable more patients to achieve LDL-C targets and help to address the current high global burden of ASCVD.

ARTICLE INFORMATION

Affiliations

Division of Cardiovascular Medicine, Department of Medicine, University of California San Diego, San Diego, CA (M.J.W.); David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA (N.E.L.); Cedars-Sinai Medical Center, Los Angeles, CA (N.E.L.); and Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD (E.D.M.).

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