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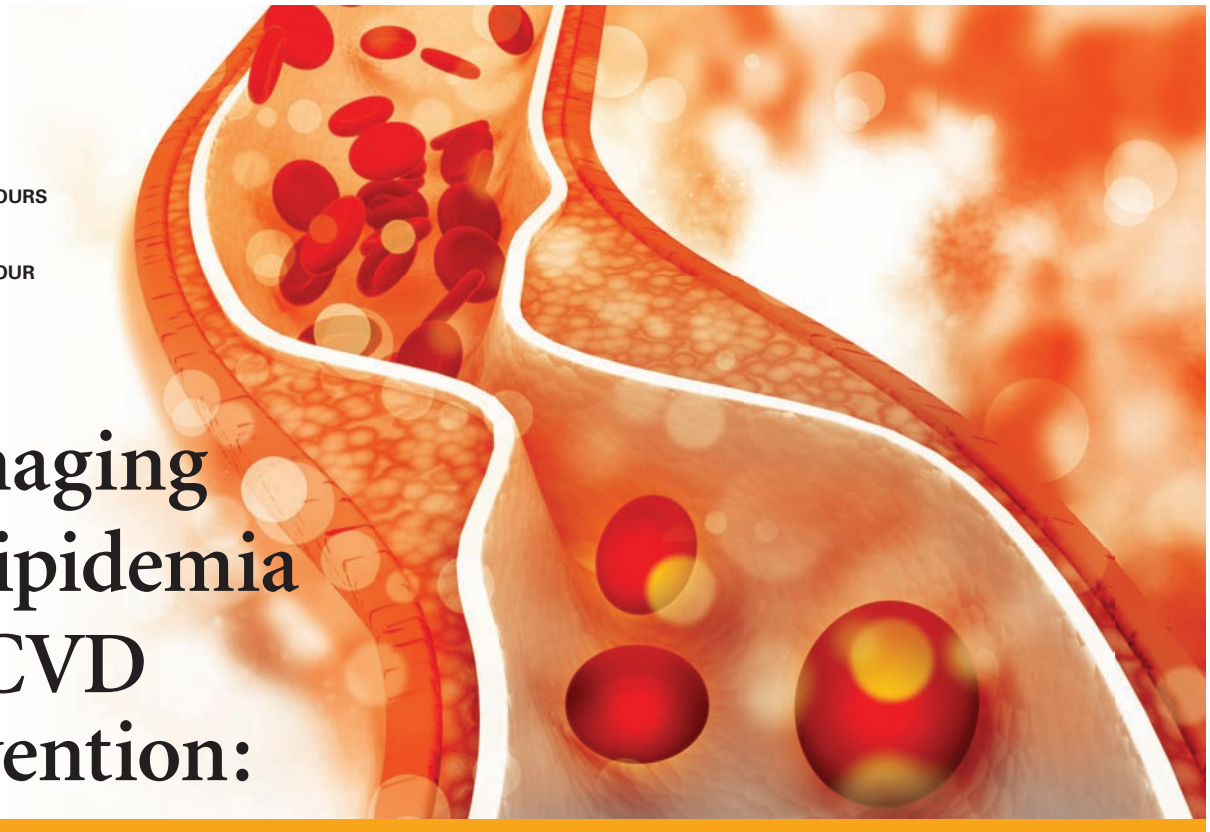

Managing dyslipidemia for CVD prevention:

A review of recent clinical practice guidelines

Abstract: The American Association of Clinical Endocrinology and the American College of Endocrinology Clinical Practice Guideline is a comprehensive, practical tool that can be used to diagnose and manage dyslipidemia, a major risk for the development and progression of atherosclerotic cardiovascular disease. Effective therapies are available to improve lipid profiles and reduce cardiovascular events.

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Despite improvements in diagnosis and management, atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of morbidity and mortality in the US, responsible for one in three deaths.[1] Because atherosclerosis is driven by atherogenic lipoproteins and inflammation, dyslipidemia is both a primary and major risk factor for development and progression of ASCVD.[2-4] Fortunately, effective therapy is available, which cannot only produce significant improvements in the lipid profile but also reduce cardiovascular (CV) events.[5,6] As new evidence becomes available, clinicians are faced with the challenge of applying the evidence and knowledge gained from these trials into clinical practice.

Clinical practice guidelines (CPGs) provide practitioners with tools to apply knowledge learned from research to clinical practice. The recently updated American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) Clinical Practice Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease use current evidence to provide a comprehensive and practical tool to diagnose and treat dyslipidemia to help prevent cardiovascular disease (CVD).[7] This article provides an overview of the 2017 AACE/ACE guideline, highlighting the unique aspects that set the guidelines apart from others in managing dyslipidemia for CVD prevention.

Overview

The AACE/ACE CPG for managing dyslipidemia and prevention of CVD was published in March 2017 as

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Keywords: cardiovascular disease prevention, clinical practice guideline, dyslipidemia, endocrinology

an update to the previous guidelines and is complementary to the AACE Diabetes Mellitus Comprehensive Care Plan.[8,9] This CPG consists of an executive summary with 87 recommendations addressing multiple aspects of medical care, such as screening recommendations for different ages (including children and adolescents), a discussion of challenges associated with atherosclerosis specific to women, risk assessment, treatment recommendations, follow-up recommendations, and monitoring.[7]

Included with each recommendation is best evidence level (BEL) score with four levels of evidence: 1 (strong), 2 (intermediate), 3 (weak), and 4 (no evidence). A recommendation grade is listed for the 87 recommendations: 45 are grade A (strong), 18 grade B (intermediate), 15 grade C (weak), and 9 grade D, signifying a lack of conclusive scientific evidence. This CPG is the first to include a cost-effectiveness rating score.[7] The appendix following the executive summary provides evidence to support the recommendations.

According to the AACE/ACE CPG's authors, the National Cholesterol Education Panel Adult Treatment Panel (NCEP ATP) forms the foundation for this CPG.[7,10] Consistent with previous CPGs, the AACE/ACE CPG continues to emphasize the importance of global risk assessment to identify an individual's risk factors for optimal personalized therapy.[7] The more risks an individual has, the greater their risk for the development and progression of ASCVD with subsequent ASCVD–related mortality.

Risk factors are often clustered and can include major risk factors, such as advancing age, elevated total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), low-density lipoprotein-cholesterol (LDL-C), a low high-density lipoprotein-cholesterol (HDL-C), diabetes mellitus, hypertension, chronic kidney disease (CKD), smoking, and family history.

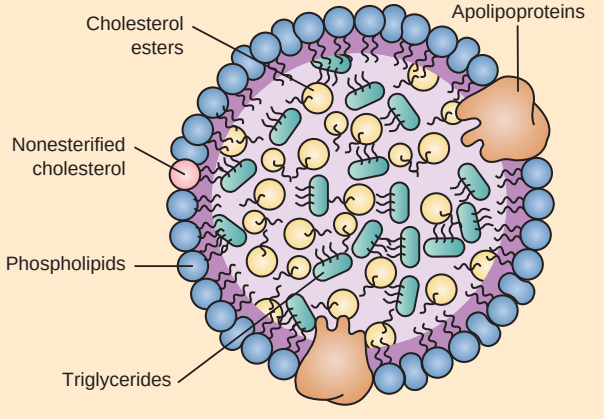
Additional risk factors that should also be taken into consideration include family history of hypercholesterolemia, lipid abnormalities associated with insulin resistance (IR), polycystic ovary syndrome, and obesity (especially abdominal). Nontraditional risks such as inherited lipid abnormalities (elevated lipoprotein [a] [Lp(a)] or apolipoprotein E4 isoform), elevated clotting factors, inflammatory markers, homocysteine, and uric acid should also be considered.

Because LDL-C is an underlying cause and independent risk for ASCVD, LDL-C remains the primary target in efforts aimed at improving lipid profiles in those at risk for ASCVD. A secondary target, non-HDL-C (calculated by subtracting HDL-C from total cholesterol) provides a simple way to estimate risk from atherogenic lipoproteins, including very low-density lipoprotein, remnants, and Lp(a). Non-HDL-C is useful for individuals with low or normal LDL-C but have elevated triglycerides (TG; 200 mg/dL or greater) and low HDL-C (grade B/BEL2).

Non-HDL-C is an equally strong or superior predictor of risk in groups of individuals with moderately elevated TG, diabetes mellitus, IR syndromes, or established coronary artery disease.[10-14] The AACE/ACE CPG is unique in its support of apolipoprotein B (apo B) or LDL particle concentration (LDL-P) as an additional measurement to refine efforts to achieve effective LDL-C reduction (Grade A/BEL1). Apo B, a reflection of LDL-P concentration, can provide a uniquely powerful assessment of total atherogenic particle burden.[7] (See *General structure of a lipoprotein.*)

To further stratify ASCVD risk, inflammatory markers such as high-sensitivity C-reactive protein (hsCRP) should be used for individuals whose standard risk assessment is borderline or in those with intermediate or higher risk with an LDL-C greater than 130 mg/dL (grade B EL2). Elevated hsCRP has been associated with increased risk for a CV event even after the adjustment

General structure of a lipoprotein



The cholesterol esters and triglycerides are located in the hydrophobic core of the macromolecule that is surrounded by an outer hydrophilic shell consisting of phospholipids, nonesterified lipoproteins, and apolipoproteins.

Source: Porth CM. *Essentials of Pathophysiology Concepts of Altered Health States.* 4th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2015:405.

of standard risk factors.[7] Another marker of inflammation, lipoprotein-associated phospholipase A2 (Lp-PLA2) can be used and has shown more specificity than hsCRP in some studies (grade A/EL1).[15-17]

CVD risk categories and goals for treatment

The LDL-C goal for an individual is determined by risk category. The AACE/ACE CPG is the first to introduce a new extreme risk category and recommends an LDL-C goal of less than 55 mg/dL, non-HDL-C less than 80 mg/dL, and apo B less than 70 mg/dL for these patients.[7]

Extreme high risk includes patients with:

- progressive ASCVD including unstable angina in patients who have achieved an LDL-C less than 70 mg/dL
- established clinical CVD in patients with diabetes mellitus or CKD stage 3 or stage 4
- familial hypercholesterolemia (FH) or history of premature ASCVD (under age 55 years [male] or under age 65 years [female]).

Patients considered for the very high-risk category are those with:

- established or recent hospitalization for acute coronary syndrome (ACS), coronary heart disease, carotid artery disease, or peripheral vascular disease, and 10-year risk greater than 20%
- diabetes mellitus or CKD stage 3 or stage 4 with one or more risk factors
- heterozygous FH.[7]

Recommended treatment goals are an LDL-C of less than 70 mg/dL, non-HDL-C less than 100 mg/dL, and Apo B less than 80 mg/dL.

High-risk patients are those with:

- two or more risk factors and 10-year risk 10% to 20%
- diabetes mellitus or CKD stage 3 or stage 4 without other risk factors.

Lipid screening recommendations in adults[7]

Young adults (men ages 20–45, women ages 20–55)
Every 5 years as part of a global risk assessment (grade C/EL4)

Middle-aged adults (men ages 45–65, women ages 55–65)
Every 1-2 years in absence of other risk factors (grade A/EL1); if risk factors present, screen more frequently based on individual circumstances and clinical judgment (grade C/EL4)

Adults >65 years of age
Annually based on risk factors (grade A/EL1)

Moderate-risk patients are those with two or fewer risk factors and a 10-year risk of less than 10%. Recommended goals for both high- and moderate-risk patients are LDL-C under 100 mg/dL, non-HDL-C less than 130 mg/dL, and Apo B under 90. Low-risk patients have no identified risk factors. Recommended lipid goals are an LDL-C less than 130 mg/dL and non-HDL-C less than 160 mg/dL.

Screening and risk assessment

A detailed risk assessment with routine screening helps place patients in the appropriate risk category (see *Lipid screening recommendations in adults*). The AACE/ACE CPG recommends using one or more of the following risk scores to determine an individual's 10-year risk of a coronary event. Each of these tools can be accessed online.

- Framingham Risk Assessment Tool (www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/). This tool calculates 10-year risk for myocardial infarction (MI). This tool can be used for adults 20 or older who do not have preexisting heart disease or diabetes.[18]
  - High-risk score: greater than 20% risk of MI or dying from coronary heart disease (CHD) in the next 10 years.
  - Intermediate risk: a 10% to 20% risk of MI or death from CHD over the next 10 years.
  - Low risk: less than 10% risk of MI or dying from CHD in the next 10 years.[7]
- Reynolds Risk Score (www.reynoldsriskscore.org) predicts 10-year risk of MI, stroke, or other major heart diseases in healthy individuals without diabetes and includes family history of premature ASCVD (either parent with MI before age 60) and hsCRP. The Reynolds Risk Score is recommended to assess women for ASCVD risk.[19]
- United Kingdom Prospective Diabetes Study (UKPDS) (www.dtu.ox.ac.uk/riskengine) is a risk engine used to calculate ASCVD risk including nonfatal and fatal CHD, and nonfatal and fatal stroke in individuals with type 2 diabetes mellitus (T2DM) not known to have heart disease. This can be used for any given duration of T2DM and is based on current age, height, weight, gender, ethnicity, smoking status, A1C levels, systolic BP, total cholesterol and HDL-C, and amount of weekly exercise.[20]
- The Multi-Ethnic Study of Atherosclerosis demonstrated that screening for subclinical disease using

rapid computed topography coronary artery calcium testing is predictive of coronary events over and above traditional risk factors in White Americans, Black Americans, Hispanics, and Chinese Americans, and can be accessed online (www.mesa-nhlbi.org/MESA-CHDRisk/MesaRiskScore/RiskScore.aspx).[21,22]

The pooled cohort risk equation recommended by the American College of Cardiology and the American Heart Association is not included.[23] According to Dr. Paul S. Jellinger, lead author of the AACE/ACE guideline, the pooled cohort risk equation overestimates risk in those with advanced age, the most heavily weighted risk factor, and underestimates risk in those with family history, elements of metabolic syndrome, and IR, such as waist circumference, impaired fasting glucose, or hypertriglyceridemia. (Paul S Jellinger, MD, MACE, oral communication, June 5, 2018.)

Treatment recommendations

A comprehensive treatment strategy aimed at metabolic abnormalities and modifiable risks is needed for an individual to meet their LDL-C goal.

Lifestyle. Lifestyle recommendations addressing fitness therapy, medical nutrition therapy, and smoking cessation remain the cornerstone of treatment. Fitness therapy should include moderate-intensity aerobic activity (4 to 7 kcal/min) four to six times per week as a 30-minute single session or as multiple sessions of at least 10 minutes at a time. Muscle strengthening activity should be performed two times per week (grade A/BEL1).[7] Medical nutrition therapy should focus on a reduced-calorie diet that includes more than five servings a day of fruits and vegetables, whole grains, fish and lean meats, limited saturated and trans fats, 2 g/day of plant stanols, and 10 to 25 g/day of fiber (grade A/BEL1).[7]

Pharmacotherapy. HMG-CoA reductase inhibitors (statins) remain the primary therapy if medical therapy is needed to achieve LDL-C goals because of their established safety and efficacy (grade A/BEL1). In both primary and secondary prevention, the benefits of statins were demonstrated by the Cholesterol Treatment Trialists' (CTT) Collaborators.[5] The CTT, a meta-analysis of 26 randomized clinical trials (involving approximately 170,000 participants) found that a 38 mg/dL reduction in LDL-C resulted in approximately 20% reduction in major CV events, 19% decrease in coronary revascularization, and 16% decrease in stroke over a period of 5 years in the studies evaluated.

Lipid screening recommendations for children and adolescents[51]

Age 3 or older if at risk for FH:
Family history of FH, premature ASCVD, or elevated cholesterol (Grade B/EL3)

Universal screening between ages 9 and 11 years and again after puberty (ages 17-21 years)

Screen adolescents over the age of 16 years every 5 years or more frequently if ASCVD risk factors are present, including family history of premature ASCVD, elements of IR syndrome

Adverse reactions associated with statin use include musculoskeletal symptoms, including myalgia without an elevation in creatine kinase (CK), myopathy with CK elevation, and rhabdomyolysis with CK levels 10 times the upper limit of normal (ULN) or greater, resulting in renal complications. Liver toxicity has also been associated with statin use with serum transaminase levels reported at three times the ULN or greater.[24]

The risk of adverse reactions may be increased in older adults, individuals with CKD, or as a result of drug interactions. For example, the statins metabolized by cytochrome P450 3A4 pathway, atorvastatin, simvastatin, and lovastatin, require special considerations because of interactions with other medications metabolized by this pathway.[7] Statins are known teratogens and should not be used in women who are pregnant or may become pregnant.[7]

The addition of nonstatin therapy should be considered for individuals with mixed dyslipidemia, those whose cholesterol is markedly increased, those who are unable to achieve their LDL-C goals with monotherapy, or for those who require lowered doses of two or more drugs to minimize adverse reactions. The cholesterol absorption inhibitor ezetimibe can be used in combination with a statin (grade A/BEL1) or as monotherapy in those individuals with limited statin tolerability (grade B/BEL2).[7] Elevation in liver enzymes have been reported when ezetimibe is used with a statin. Ezetimibe is not recommended in patients with moderate or severe hepatic impairment. Myopathy and rhabdomyolysis have been reported when ezetimibe is used alone or in conjunction with a statin.[24]

The new class of proprotein convertase subtilisin/kexin (PCSK9) inhibitors, evolocumab or alirocumab, should be considered for individuals with FH (grade

A/BEL1) and for those with clinical CVD on maximally tolerated statins who are not able to meet their LDL-C and non-HDL-C goals (grade A/BEL1). If TG are severely elevated (greater than 500 mg/dL), the AACE/ACE CPG recommends the addition of a fibrate or 2 to 4 g/day prescription omega-3s.[7] Because nonprescription omega-3 dietary supplements are not FDA approved, patients should be advised not to use them. Fibrates have been associated with an increase in creatinine levels, although the mechanism by which this occurs is not clear.[7]

Myositis, myalgia, and myopathy with rhabdomyolysis have been reported with fibrates. This risk is increased when used with a statin.[7] Niacin should be used as an adjunct to TG reduction but not for individuals whose lipids are aggressively treated with statins due to the lack of benefit seen in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) and Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) clinical trials.[25,26]

Follow-up and monitoring

Lipid status should be reassessed 6 weeks after therapy initiation and again at 6-week intervals until the treatment goal is achieved (grade D/BEL4). Apo B and LDL-P number are useful to verify the lipid goals beyond LDL-C have been achieved. Both Apo B and LDL-P reflect the total amount of circulating atherogenic particles and are more closely associated with IR syndromes than LDL-C or non-HDL-C when TG are elevated and HDL-C is low (grade A/BEL1). An Apo B greater than 130 mg/dL with LDL-C less than 160 mg/dL with or without elevated TGs is associated with premature ASCVD.[27]

When goals have been achieved, lipid status should be monitored every 6 to 12 months depending on adherence and consistency in results. Situations that warrant more frequent monitoring include deterioration of diabetes control, change in medication or medical condition predisposing to secondary dyslipidemia, new ASCVD risk factor, or as new evidence emerges (grade C/BEL4). Consultation to a certified lipid specialist or an endocrinologist is recommended for patients with lipid abnormalities on intensive treatment, when T2DM and dyslipidemia coexist, or if atherothrombotic disease progresses despite favorable lipid levels.

Special populations

Familial hypercholesterolemia (FH) is a genetic disorder resulting in abnormally high levels of LDL-C and premature ASCVD. FH is caused by a partial or full inhibition of LDL receptor activity because of a gene mutation inherited from one parent; this results in heterozygous FH (HeFH) or from gene mutations inherited from both parents resulting in homozygous FH (HoFH). HoFH is rare, with prevalence estimated to be 1 in 160,000 to 250,000 individuals.[7] Individuals with HoFH can have LDL-C levels over 500 mg/dL and early-onset ASCVD that could manifest in childhood depending on severity of LDL-C.[28-31] HeFH is more prevalent and is estimated to affect 1 in 200 to 250 individuals.[7] LDL-C levels in HeFH range from 90 mg/dL to 500 mg/dL. HeFH is also associated with premature ASCVD with first CV event at age 42.[28]

Screening for FH should be performed when there is a family history of premature ASCVD or elevated cholesterol LDL-C greater than 190 mg/dL (grade C/BEL4). The criteria for a diagnosis of FH include lipid levels, family history, physical exam findings for signs such as tendon xanthomas or full corneal arcus in patients younger than age 40, or genetic analysis if available. The Simon Broome Register Diagnostic Criteria, the Dutch Lipid Clinic Network Diagnostic Criteria for FH, and the US Make Early Diagnosis to Prevent Early Deaths Programs Diagnostic Criteria are clinical tools to support diagnosis.[28,31]

Diabetes mellitus as CVD equivalent. ASCVD is the most common cause of death in adults with diabetes. Because aggressive CVD risk factor management is required, patients with T2DM are categorized into high, very high, or extreme risk categories depending on the number of additional risk factors.[32] Special attention should be given to those with type 1 diabetes mellitus (T1DM) as well. Individuals with T1DM over age 15 years or with two or more CVD risk factors should be treated aggressively, as with those with T2DM. Other factors that increase risk in T1DM include albuminuria, previous history of MI, IR, or metabolic syndrome, and hsCRP greater than 3 mg/L.[7,33-42]

CKD as CVD equivalent. Similar to diabetes, CVD is a leading cause of death in patients with CKD and, like diabetes, it is considered a CV equivalent.[7] Patients with CKD stage 3 or stage 4 require aggressive risk factor reduction and should be categorized into high, very high, or extreme risk categories depending on how many additional risk factors they have. In addition to

traditional risk factors, patients with CKD have increased prevalence of CKD-related risk, including but not limited to, the type of CKD, proteinuria, oxidative stress, elevated homocysteine, and uremic toxins.[43]

Challenges specific to women. Although ASCVD is the leading cause of mortality for women in the US, women are less likely to be offered treatment for dyslipidemia.[44] Women may present with subtle or atypical symptoms, resulting in delays in evaluation and diagnosis.[45,46] When symptoms suggestive of ischemia are present, angiography may reveal normal or near-normal coronary arteries. Traditional diagnostics may be less accurate in women because of differences in anatomy, hormonal milieu, advanced age at onset, and increase in comorbidities upon presentation.[45,46]

Special attention should be given to assessing women for ASCVD. The Reynolds Risk Score or the Framingham Risk Assessment Tool is beneficial to determine 10-year risk. If unable to meet goals based on their ASCVD risk category with lifestyle alone, women should be treated with medical therapy (grade C/BEL4). In both the Women's Health Initiative and the Heart and Estrogen/progestin Replacement Study (HERS), hormone replacement therapy failed to demonstrate protection against CVD, so it is not recommended in postmenopausal women (grade A/BEL1).[7]

Special issues for children and adolescents

Atherosclerosis caused by abnormal lipid levels can begin as early as childhood and is prognostic of lipid abnormalities and ASCVD later in life.[47-55] Therefore, lipid abnormalities should be diagnosed and managed as early as possible (see *Lipid screening recommendations for children and adolescents*). Interpreting lipid profiles in children and adolescents can be a challenge, and the following should be considered:

- Gender differences: girls tend to have significantly higher mean total cholesterol and LDL-C levels than boys
- Fluctuations during childhood and adolescents: lipid levels peak before puberty in males (ages 9 to 11 years) and then decrease in puberty nearing adult levels
- Low HDL-C does not reflect IR in childhood; obesity and triglycerides are better indicators.[56-59]

The value of setting goals

The AACE/ACE CPG recommends setting lipid goals to manage dyslipidemia. The CPG authors believe it is important to set goals to provide strong incentives for both patients and clinicians.[60] Goals are used to manage other CV risks, such as BP goals for hypertension and A1C goals for diabetes management. However, setting LDL-C and non-HDL-C goals for dyslipidemia management has been controversial.[60]

Results from clinical trials suggest the benefits from statins depend on the extent of the LDL-C reduction achieved.[61] Patient response to statins may vary based on a variety of factors. Maximally tolerated statins alone may not provide adequate LDL-C reduction. Furthermore, many patients with high, very high, or extreme CVD risk may not be able to tolerate the higher-intensity statin dose needed to achieve adequate LDL-C reduction. Goals help patients and providers to recognize the threshold in which nonstatin therapies may be required for adequate LDL-C reduction.

LDL-C target: Lower is better

Targeting LDL-C to a goal of less than 55 mg/dL for patients in the extreme risk category is a unique feature of the AACE/ACE CPG. The rationale for the new extreme risk category and treatment goal are based on the ASCVD benefit demonstrated in the landmark Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study.[7,62] The study enrolled 18,144 patients with recent (previous 10 days) ACS with a median follow-up of 6 years. Subjects were randomized to simvastatin 40 mg versus simvastatin 40 mg plus ezetimibe 10 mg. The primary composite endpoint was CV death, nonfatal MI, unstable angina requiring hospitalization, coronary revascularization, or nonfatal stroke.

Subjects receiving simvastatin and ezetimibe achieved lower LDL-C than those receiving simvastatin alone (LDL-C 53.7 mg/dL versus 69.5 mg/dL, respectively), with a reduction in primary composite endpoint (HR 0.936, 95% CI 0.89 to 0.99) and an absolute reduction in rate of primary endpoint at 7 years (32.7 versus 34.7). Adverse reactions were similar in both arms.

Additional support for the extreme risk category was provided by a subanalysis of IMPROVE-IT that found an even more pronounced CV benefit among the 4,933 subjects with ACS and diabetes compared with the 13,302 patients who were not diabetic.[63] Subjects with diabetes receiving simvastatin and ezetimibe saw greater reduction in LDL-C than those who did not have diabetes at 1 year, achieving LDL-C 43 mg/dL reduction in LDL-C versus 23 mg/dL reduction, respectively. Unlike patients without diabetes, those with diabetes

receiving simvastatin and ezetimibe had a 14% reduction in primary endpoint, 21% reduction in MI, and 42% reduction in stroke.[63] Interestingly, key differences were noted between patients with diabetes versus those without diabetes. Those with diabetes had higher risk features, including a higher body mass index, advanced age, and a history of CVD. These patients had lower LDL levels and were more likely to be treated with statins.[63]

The relationship between LDL-C and CVD

Most experts believe the benefit seen in the IMPROVE-IT study and the subanalysis was due to the additional LDL-C reduction.[60] Clinical trials with lipid-lowering therapy have demonstrated a continuous positive relationship between coronary disease risk and blood cholesterol concentrations with a 20% reduction of vascular events including coronary death, nonfatal MI, coronary revascularization, or stroke for every 40 mg/dL reduction in LDL-C.[5]

As previously mentioned in the CTT collaboration, a 38.7 mg/dL reduction in LDL-C results showed a 24% reduction in first major CV event. At 1 year of treatment, those on standard statin regimens lowered their LDL-C by 41.4 mg/dL, and those receiving intensive statin therapy achieved an additional 19.7% reduction in their LDL-C.[5] A subanalysis of standard versus intensive statin regimens demonstrated benefit even if baseline LDL-C was low. For those with baseline LDL-C less than 77 mg/dL, every 38.7 mg/dL in LDL-C reduction corresponded to an approximate 29% reduction in major CV events, and when baseline LDL-C was under 70 mg/dL, every 38.7 mg/dL reduction resulted in 37% decrease in events.[5,7]

A meta-analysis of individual patient data from eight randomized controlled trials with statins including pravastatin, lovastatin, fluvastatin, atorvastatin, and simvastatin confirmed CTT results.[61] Patients who achieved an LDL-C under 50 mg/dL had a significantly lower risk of a major CV event than those achieving an LDL-C between 75 mg/dL to 100 mg/dL (adjusted hazard ratio 0.81; 95% CI 0.70 to 0.95).

Results from the Further Cardiovascular Outcomes Research and PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) provide further support for aggressive LDL-C reduction in patients with the most risk.[6] FOURIER compared evolocumab added to statin versus statin therapy in 22,500 patients with dyslipidemia and ASCVD (defined as coronary artery disease, peripheral arterial disease, or stroke) who were at increased risk for recurring events. Participants were optimized on statin therapy with LDL-C 70 mg/dL or greater or non-HDL-C 100 mg/dL or greater. The primary endpoint included composite of time to first CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. Secondary endpoint included composite of time to first CV death, MI, and stroke. Subjects treated with evolocumab in addition to statin had 15% reduction in primary endpoint and 20% reduction in secondary endpoint.

Lowering LDL-C

If "lower is better" when it comes to LDL-C, is there a limit to how much providers should lower LDL-C? Now that therapy is available to achieve very low LDL-C, both patients and providers need to question if a low LDL-C may have adverse consequences. The FOURIER trial provides insight to this question. In FOURIER, evolocumab added to statin reduced LDL-C levels by 63% by week 12, achieving a median LDL-C of 26 mg/dL. Forty-seven percent of patients treated with evolocumab and statin achieved an LDL-C under 25 mg/dL. Adverse reactions in the evolocumab group were similar to placebo with no increase in adverse reactions in those who achieved LDL-C as low as 25 mg/dL.[64]

EBBINGHAUS, a substudy of FOURIER, followed 1,204 patients for median of 19 months to assess cognitive function.[64] The primary endpoint was the score on spatial working memory strategy index of executive function and the secondary endpoints were the scores for working memory, episodic memory, and psychomotor speed. The study found that evolocumab was not inferior to placebo on the selected cognitive function domains assessed. No significant differences between groups were found in the secondary endpoints. Mean changes in baseline score were similar within study groups, including the 661 subjects with LDL-C under 25 mg/dL.[64]

Conclusion

The publication of the AACE/ACE CPG was placed on hold until the FOURIER trial results were published in March of 2017 (Paul S Jellinger, MD, MACE, oral communication, June 5, 2018). The results of FOURIER validated the AACE/ACE recommendations, which have been enthusiastically accepted. The evidence clearly supports that not only is "lower better" but that patients

with the most risk can benefit from aggressive LDL-C lowering. The introduction of the extreme risk category in the AAACE/ACE CPG helps providers better identify these patients. Although guidelines are not a substitute for a provider's medical decision-making based on needs specific to a patient, applying this CPG to practice provides both a comprehensive and personalized approach to dyslipidemia management to reduce CV events.

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