MAYO CLINIC

How Low to Go With Lipid-Lowering Therapies in a Cost-effective and Prudent Manner

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Abstract

The 2013 American College of Cardiology/American Heart Association guideline on the treatment of blood cholesterol was a landmark document guiding health care professionals around the globe on how to administer lipid-lowering therapies. Those guidelines were primarily focused on statin therapy benefit groups. The writing committee found insufficient evidence for specific low-density lipoprotein cholesterol (LDL-C) treatment targets. There have been many important updates in the lipid literature since the publication of that document. Most importantly, clinical trials have provided definitive evidence for the pivotal role of LDL-C in atherogenesis and the improvement in clinical outcomes by means of aggressive LDL-C reduction. Ezetimibe, evolocumab, and alirocumab treatment resulted in substantial reductions in major adverse cardiovascular outcomes. These data encourage a discussion on whether LDL-C targets are warranted in primary and/or secondary prevention, and if so, how low should those targets be. In order to answer such questions, the costs and safety of such therapies, as well as the safety of very low levels of LDL-C need to be addressed. This review discusses the relationship between LDL-C lowering and cardiovascular risk reduction, the efficacy, safety, and cost-effectiveness of high-intensity lipid-lowering therapies, and the recommendations from the most recent lipid guidelines.

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Epidemiological studies and clinical trials have consistently shown a dose-dependent association between low-density lipoprotein cholesterol (LDL-C) and cardiovascular (CV) risk.[1] Similarly, genetic polymorphisms resulting in lifelong exposures to low LDL-C levels are associated with a reduction in coronary heart disease (CHD) risk that is proportional to the magnitude of LDL-C lowering.[2]

Statins are the primary pharmacotherapy for LDL-C reduction and prevention of adverse CV outcomes. The magnitude of the long-term clinical benefit and risk reduction with statin therapy is directly proportional to the absolute reduction in LDL-C levels. After the first year of statin use, each 38.6 mg/dL (to convert to mmol/L, multiply by 0.0259) of reduction in LDL-C leads to a 20% to 25% relative reduction of global CV risk, including a 20% relative decrease in CHD mortality.[3,4]

PRINCIPLES OF LIPID-LOWERING THERAPY, REDUCTION OF LDL-C, AND CV RISK

Two key concepts drive the relationship between prescribed lipid-lowering therapies and the anticipated risk reduction in an individual patient. First, the absolute mg/dL reduction in LDL-C is largely dependent on baseline LDL-C level and the dose and potency of lipid-lowering therapy (Figure 1). For example, high-intensity statins such as atorvastatin, 80-mg, and rosuvastatin, 40-mg, daily are expected to reduce LDL-C levels by approximately 50%, regardless of baseline levels.[4] Doubling the dose of any given statin is expected to further reduce LDL-C by 4% to 7%.[5] Ezetimibe, when added to statins, typically reduces LDL-C levels by an additional 20% to 25%.[6,7] The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors evolocumab and alirocumab reduce LDL-C levels by approximately 60%.[6,8]

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Second, the absolute risk reduction (ARR) or net benefit achieved by an individual patient with lipid-lowering therapies is highly dependent on baseline CV risk. An example is illustrated in Figure 2. Consider 2 patients who will be starting lipid-lowering therapies—patient A has a 10-year estimated risk of 20%, whereas patient B has a predicted risk of 4%. If both patients attain a similar reduction in LDL-C of 40 mg/dL from baseline, both will achieve a 25% relative reduction in CV risk. This reduction will translate into a 5% ARR for patient A but only a 1% ARR for patient B.

Cardiovascular specialists and primary care physicians prescribing lipid-lowering therapies should commit time and resources into communicating these concepts effectively with patients in shared decision making. Several studies have found that patient adherence to statin therapy falls short of 50% within 1 year of prescription.[9] Clinical decision aids are available and have been reported to improve patient knowledge, although definitive data reporting improved long-term adherence to statin therapy is not available.[10]

RISK PREDICTION TOOLS

In primary prevention, there are several validated CV risk estimation systems, such as the Framingham Heart Study algorithm,[11] the SCORE (Systematic Coronary Risk Evaluation) system,[12] the QRISK score,[13] and the Pooled Cohort Equations (PCE).[14] Most risk prediction tools perform well when applied to populations similar to those from which they were derived.[15] The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the treatment of blood cholesterol recommend using the PCE to estimate 10-year atherosclerotic CV disease (ASCVD) events.[16] The PCE was derived from 4 prospective studies that enrolled patients between 1968 and 1990.[17] In more contemporary cohorts, the PCE appears to overestimate risk by as much as 60% to 90%.[17,18] Some investigators have proposed recalibration of the PCE with updated ASCVD incidence rates to better match predicted and observed risk.[17-19]

ARTICLE HIGHLIGHTS

- Epidemiological and clinical trial data have consistently shown a linear association between low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular (CV) risk.
- Each reduction of LDL-C by 38.6 mg/dL (to convert to mmol/L, multiply by 0.0259) is associated with approximately 20% to 25% relative reduction in global CV risk in patients treated with statin therapy, ezetimibe, or proprotein convertase subtilisin/kexin type 9 inhibitors.
- The absolute reduction in CV risk with lipid-lowering therapies is determined by baseline LDL-C level, potency and dose of the lipid-lowering agent, and particularly the baseline CV risk.
- Over recent years, randomized trials of ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors found a reduction in CV risk by lowering LDL-C below levels previously considered "acceptable" (eg, 70 mg/dL), with reassuring safety results. These data support the use of more aggressive lipid-lowering strategies, particularly in patients at high CV risk or in those with substantially elevated LDL-C levels.
- In order to reduce patients' CV risks in a cost-conscientious manner, health care professionals should (1) advocate for aggressive implementation of healthy lifestyle changes, (2) advise maximally tolerated statin therapy for all patients meeting indications, and (3) reserve the newer lipid-lowering agents for the highest-risk patients with persistently elevated LDL-C levels.

The PCE is also particularly sensitive to chronological age because of the inclusion of stroke in the composite of ASCVD outcomes. Nearly all men older than 65 years old and women older than 70 years will be classified as high-risk based on the PCE. Although these patients are at higher risk for ASCVD, there is limited data to support the initiation of lipid-lowering therapies for primary prevention in the elderly population.[16] Furthermore, more than one-third of strokes are not atherosclerotic but rather cardioembolic.[20] It is unlikely that lipid lowering would prevent nonatherosclerotic strokes, which raises the question of whether the risk of these events should be utilized to guide primary prevention lipid therapy. Notwithstanding these limitations, the PCE has several benefits, including ease of use,

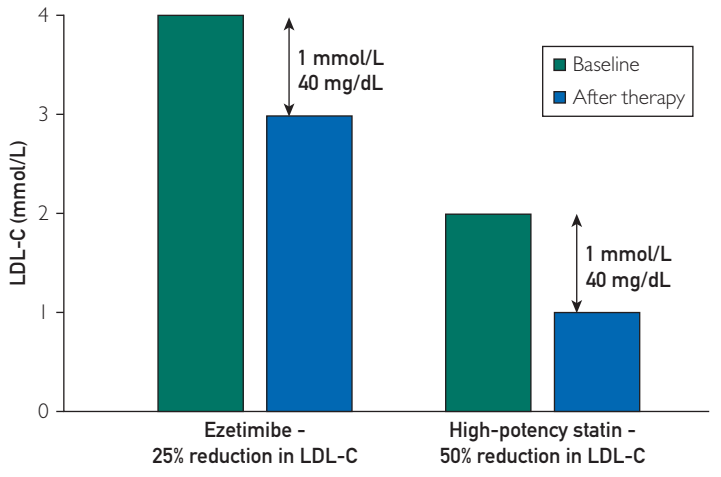

FIGURE 1. The reduction in low-density lipoprotein cholesterol (LDL-C) with lipid-lowering agents depends on baseline LDL-C level and the potency of therapy. A similar reduction in LDL-C of 40 mg/dL (1 mmol/L) can be achieved with ezetimibe if the baseline LDL-C level is 160 mg/dL (4 mmol/L) or with a high-potency statin if baseline LDL-C is 80 mg/dL (2 mmol/L).

race-specific beta coefficients, and the possibility of estimating lifetime CV risk, which provides clinicians with an additional tool to motivate lifestyle changes, particularly in younger individuals.[14]

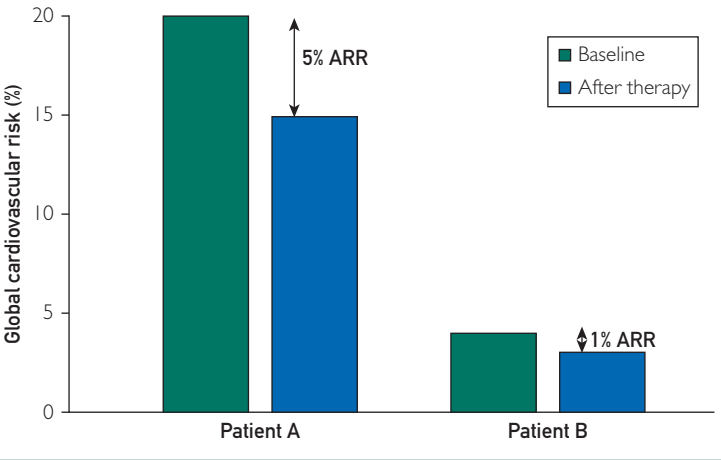

FIGURE 2. Two patients with similar degrees of low-density lipoprotein cholesterol reduction (40 mg/dL or 1 mmol/L) and relative risk reduction (25%). Patient A has a baseline risk of 20% and achieved an absolute risk reduction (ARR) of 5%. Patient B has a baseline risk of 4% and achieved an ARR of 1%.

The SCORE risk was derived from 12 prospective studies from 11 European countries, with a sample size of approximately 200,000 individuals. It is recommended in European guidelines and includes different versions for use in high- and low-risk countries. SCORE estimates the 10-year risk of CV mortality. Nonfatal end points are excluded from SCORE calculator in order to provide a more objective outcome, with widely available data allowing for more frequent recalibrations as time lapses and risk evolves.[12,15]

The United Kingdom's National Institute of Health and Care Excellence recommends the QRISK prediction tool. The QRISK score is derived from data collected from general practitioner databases in the United Kingdom from 1993 to 2008. It was developed based on data from more than 2 million individuals. The QRISK system is very comprehensive, including social determinants of health, such as postal code, and family history of CHD.[13]

The aforementioned risk prediction tools do not include coronary artery calcium (CAC) scoring as a variable for risk estimation. The CAC score is a direct measurement of subclinical atherosclerosis, with the potential to provide additional risk stratification, particularly in intermediate-risk patients such as those with a 10-year ASCVD risk between 5% and 20% by the PCE. In this population, approximately 40% to 50% have a CAC score of zero, and the presence of mild to moderate CAC is associated with a 2- to 5-fold increase in ASCVD events compared with a CAC of zero.[21]

In conclusion, risk prediction scores from around the globe have various strengths and weaknesses but perform better when applied to populations similar to the derivation cohort. Cardiovascular physicians should use the risk assessment tool most relevant to the population and location of practice. In intermediate-risk patients or when the risk is uncertain (eg, risk factors not accounted for in prediction scores), clinicians may consider CAC for better risk stratification. Finally, physicians should engage in shared decision making to develop an optimal plan in partnership with the patient.

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NONSTATIN THERAPIES

The 2013 ACC/AHA guideline on the treatment of blood cholesterol did not recommend routine use of non-statin drugs for the reduction of CV events.[16] More recently, however, randomized data for ezetimibe and the PCSK9 inhibitors evolocumab and alirocumab have documented improved CV outcomes through LDL-C reduction in patients already treated with a statin. In fact, the reduction in the risk of major CV outcomes observed with PCSK9 inhibitors and ezetimibe is largely consistent with the benefits of statin therapy on the basis of relative risk reduction per mg/dL of LDL-C lowering.[6,22]

In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study, 18,144 patients with a recent acute coronary syndrome and baseline LDL-C level of 50 to 125 mg/dL were randomized to daily placebo or ezetimibe, 10 mg, in addition to simvastatin, 40 mg.[6] During a median follow-up of 6 years, the average LDL-C level was 16 mg/dL lower in the ezetimibe group: 54 vs. 70 mg/dL. The observed 6% to 7% relative risk reduction in the composite CV outcome is consistent with the expected risk reduction seen with statins and similar degrees of LDL-C reduction.[6] The benefit of ezetimibe was particularly enhanced in the highest-risk patients, such as those with diabetes, peripheral arterial disease (PAD), chronic kidney disease, age greater than 75 years, and prior coronary artery bypass graft surgery.[6,23]

In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, 27,564 patients with ASCVD and LDL-C levels of 70 mg/dL or higher while taking statins were randomized to biweekly or monthly injections of placebo or evolocumab. After a median follow-up of 2.2 years, evolocumab reduced LDL-C levels by 59% or 56 mg/dL compared with placebo, from a baseline of 92 mg/dL to 30 mg/dL. This change resulted in a 15% relative risk reduction in the primary composite CV end point, consistent with the expected risk reduction per LDL-C lowering over 2 years as predicted by the Cholesterol Treatment Trialists Collaboration.[22] Similar to ezetimibe, the ARR achieved with evolocumab was larger in the patients at highest risk, such as those with PAD, multiple prior myocardial infarctions (MIs), or with residual multivessel CHD.[24,25]

The Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY OUTCOMES) trial enrolled 18,924 patients with an acute coronary syndrome within 1 to 12 months before enrollment and inadequate lipid control (LDL-C, ≥70 mg/dL; non–high-density lipoprotein cholesterol, ≥100 mg/dL [to convert to mmol/L, multiply by 0.0259]; or apolipoprotein B, ≥80 mg/dL [to convert to g/L, multiply by 0.01]) despite high-intensity statin therapy. Patients were randomized to subcutaneous placebo or alirocumab for a goal LDL-C of 25 to 50 mg/dL. After a median follow-up of 2.8 years, LDL-C levels were on average 63% lower in the alirocumab group (38 mg/dL vs 93 mg/dL in the placebo group). Further, there was a significant reduction in the combined end point of CHD death, MI, ischemic stroke, and unstable angina with alirocumab (9.5%) compared with placebo (11.1%). All-cause mortality was also significantly lower with alirocumab (3.5%) relative to placebo (4.1%).[26]

LDL-C TARGETS VS THRESHOLDS FOR ADDITIONAL THERAPY

The 2013 ACC/AHA guideline on the treatment of blood cholesterol did not recommend for or against the routine use of LDL-C or non–high-density lipoprotein cholesterol treatment goals. Rather, the committee identified groups of patients known to benefit from statins and focused on attainment of percentage LDL-C reductions (eg ≥50%).[16] Notwithstanding the absence of specific therapeutic goals in randomized studies, the data on ezetimibe, PCSK9 inhibitors, and studies of higher- vs lower-intensity statin do in fact support the notion that “lower is better” with clinically proven

therapies. In fact, PCSK9 inhibitor data would suggest that even patients considered to have "acceptable" LDL-C levels (eg, 70 mg/dL) can derive substantial benefit from aggressive LDL-C lowering (eg, down to 30 mg/dL) and obtain robust reduction in CV risk, particularly in high-risk individuals. Therefore, more recent guidelines have supported more aggressive lipid-lowering strategies and LDL-C goals (see "Guideline Recommendations for Statin and Nonstatin Therapies" section).

Importantly, the accuracy of LDL-C estimation by the standard Friedewald equation has been called into question, particularly at low levels of LDL-C. The Friedewald formula uses a fixed factor of 5 for the ratio of triglycerides to very low-density lipoprotein cholesterol (VLDL-C); the true value of this ratio, however, varies substantially based on triglyceride and cholesterol levels.[27] A novel (Martin/Hopkins) method for LDL-C estimation using a variable ratio of triglycerides to VLDL-C factor has improved accuracy relative to the Friedewald formula, particularly in patients with LDL-C levels lower than 70 mg/dL.[27] This finding has been reproduced in several external validation cohorts and consequently adopted by several laboratories, such as Quest Diagnostics, as standard of care for LDL-C estimation.[28,29] Approximately 20% of individuals with Friedewald-estimated LDL-C levels less than 70 mg/dL have a more accurate value of 70 mg/dL or higher using the novel equation.[28] This difference has important implications in this new era of aggressive lipid-lowering therapies, particularly for secondary prevention in higher-risk patients in whom an LDL-C level of 70 mg/dL is no longer considered acceptable.

SAFETY

To answer the question on exactly how low the LDL-C targets should be, 2 important concepts must be addressed: (1) the safety of intensive lipid-lowering therapies and VLDL-C levels and (2) the cost-effectiveness of such therapies.

Notably, myopathy, new-onset diabetes, and a slight increase in hemorrhagic strokes can be seen with statins. Myalgias, weakness, and other nonspecific muscular symptoms can occur in up to one-third of statin-treated patients.[30,31] True myopathy with elevated creatinine kinase levels and rhabdomyolysis are exceedingly rare, with incidences of 1 to 5 per 10,000 person-years and 2 to 5 per 100,000 person-years, respectively.[3,4,32] There is an approximate 10% relative risk increase of new-onset diabetes in statin-treated patients,[33] although such risk is primarily restricted to patients with risk factors for development of diabetes (overweight, glucose intolerance, or with other metabolic syndrome traits).[34] In the Justification for the Use of Statins in Prevention: an Interventional Trial Evaluating Rosuvastatin (JUPITER) study, there was substantial risk reduction and a clear net benefit in those newly diagnosed with diabetes.[34] In general, approximately 4 to 5 ASCVD events are prevented for every 1 incident case of diabetes.[35]

Results from the Cholesterol Treatment Trialists Collaboration revealed an odds ratio of 1.21 for hemorrhagic stroke in statin vs placebo-control trials. This risk was primarily driven by the population with a history of ischemic stroke.[3,36] This finding was not confirmed in a larger meta-analysis comprising more than 180,000 patients from randomized trials.[37] There is still a large net benefit of statins even in populations at risk for hemorrhagic stroke.[3,34] Observational data suggesting increased risk of cognitive impairment with low LDL-C levels have not been confirmed in randomized studies.[22,30]

Similarly, treatment of low LDL-C with ezetimibe and PCSK9 inhibitors have not had significant safety hazards in clinical trials.[6,22] There were no differences between evolocumab or alirocumab compared with placebo in their respective trials with regard to myopathy, muscle-related events, new-onset diabetes, malignancy, steroid or gonadal hormonal levels, or cognition despite a mean LDL-C of approximately 30 mg/dL and 53 mg/dL during a mean follow-up of 2.2 and 2.8 years, respectively.[6,22,38] Definitive conclusions about

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TABLE. Summary of Recent Guidelines for Lipid Management and Prevention of Atherosclerotic Cardiovascular Outcomes[a]

Guidelines	Indications for statins	Indications for nonstatin therapy[c]	LDL-C targets
2016 ACC expert consensus pathway on the role of nonstatin therapies for LDL-C lowering[46] and 2017 focused update[47]	A. Age ≥21 y, clinical ASCVD B. Age ≥21 y, LDL-C ≥190 mg/dL C. DM, age 40-75 y, LDL-C 70-189 mg/dL D. ASCVD risk ≥7.5% (PCE) in adults 40-75 y without DM or ASCVD, LDL-C 70-189 mg/dL	1. Indications A-B: consider ezetimibe, PCSK9 inhibitors, and BAS in ezetimibe-intolerant patients who do not achieve LDL-C targets 2. Indications C-D: consider ezetimibe and BAS in ezetimibe-intolerant patients who do not achieve LDL-C targets 3. Before adding nonstatin therapies, evaluate adherence and lifestyle, engage in shared decision making, and consider the desired relative reduction in LDL-C	1. Indication A: aim for ≥50% LDL-C reduction. May consider LDL-C ≤70 mg/dL or non—HDL-C <100 mg/dL 2. Indications B-C: aim for ≥50% LDL-C reduction. May consider LDL-C ≤100 mg/dL or non—HDL-C <130 mg/dL 3. Indication D: aim for ≥30% LDL-C reduction if no high-risk markers or ≥50% LDL-C reduction if high-risk markers. May consider LDL-C ≤100 mg/dL or non—HDL-C <130 mg/dL
2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia[48]	A. Clinical atherosclerosis B. DM, age >40 y, duration >15 y and age >30 y, or microvascular complications C. CKD, GFR <60 mL/min/1.73 m^2 D. LDL-C ≥193 mg/dL or documented FH E. High FRS ≥20% F. FRS 10%-19% if LDL-C ≥140 mg/dL, non-HDL-C ≥170 mg/dL, apoB ≥1.2 g/L, men ≥50 y and women ≥60 y with additional risk factors	1. Indications A-D: consider ezetimibe, BAS (alternative), or PCSK9 inhibitors if targets not achieved 2. Indications E-F: consider ezetimibe (first line) or BAS (alternative) if targets not achieved	1. ≥50% reduction in LDL-C, LDL-C <77 mg/dL, apoB <0.8 g/L, or non—HDL-C <2100 mg/dL
2016 European guidelines on cardiovascular disease prevention n clinical practice[15] and 2017 update of ESC/EAS Task Force on practical clinical guidance for PCSK9 inhibition[49]	A. Known ASCVD, DM with target-organ damage, CKD GFR <30 mL/min/1.73 m^2, SCORE >10% B. LDL-C ≥70 mg/dL and: markedly elevated risk factors, total cholesterol >310 mg/dL, BP >180/110 mm Hg, DM without target-organ damage, CKD GFR 30-59 mL/min/1.73 m^2, or SCORE >5%-10% C. LDL-C ≥100 mg/dL and SCORE 1%-5% D. LDL-C ≥190 mg/dL and SCORE <1%	1. Ezetimibe monotherapy in statin-intolerant patients. Ezetimibe with statin when LDL-C goals are not met on maximally tolerated statin 2. PCSK9 inhibitor in patients with known ASCVD with LDL-C >140 mg/dL or LDL-C >100 mg/dL if additional indices of risk severity (FH, multivascular, rapidly progressive ASCVD, DM with target-organ damage) despite maximally tolerated statin with or without ezetimibe 3. PCSK9 inhibitor if FH without ASCVD with LDL-C >180 mg/dL or LDL-C >140 mg/dL if additional indices of risk severity despite maximally tolerated statin/ezetimibe	1. In patients at very high CV risk, the LDL-C goal is <70 mg/dL or a reduction of ≥50% if the baseline is between 70-135 mg/dL 2. In patients at high CV risk, the LDL-C goal is <100 mg/dL or a reduction of ≥50% if the baseline is between 100-200 mg/dL 3. In other patients receiving LDL-C—lowering treatment, an LDL-C goal of <115 mg/dL should be considered

[a]ACC = American College of Cardiology; apoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; BAS = bile acid sequestrants; BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; DM = diabetes mellitus; EAS = European Atherosclerosis Society; ESC = European Society of Cardiology; FH = familial hypercholesterolemia; FRS = Framingham risk score; GFR = glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PCE = Pooled Cohort Equations; PCSK9 = proprotein convertase subtilisin/kexin type 9; SCORE = Systematic Coronary Risk Estimation.

[c]When targets are not achieved, confirm adherence and barriers to statin use, reinforce behavioral modifications, and discuss add-on therapies with patient.

[b]SI conversion units: To convert LCL-C and HDL-C values to mmol/L, multiply by 0.0259.

the long-term safety of PCSK9 inhibition should await long-term follow-up results. Injection site reactions are more common with PCSK9 inhibitors compared with placebo injections.[8,22]

COST-EFFECTIVENESS

The cost-effectiveness of lipid-lowering therapies is highly dependent on drug costs. With statin therapy, the cost ranges widely, from a newer branded agent like Livalo (pitavastatin) with an average retail price of about $320 per month ($3840 per year) to $4 to $10 per month ($48-$120 per year) for generic statins. If generic statins are effectively employed in practice, it may not only be cost-effective but also cost-saving in higher-risk individuals. Heller et al[39] estimated that over a 10-year period, the 2013 ACC/AHA cholesterol guidelines would result in 12.3 million additional statin users, a gain of 183,000 quality-adjusted life-years (QALYs), and savings of $3.8 billion in the United States compared with the previous Adult Treatment Panel III guidelines.

The high cost of nonstatin therapies yields a less favorable cost-effectiveness profile. In a model of the US adult population, ezetimibe demonstrated potential to prevent 2.7 million major adverse CV events over 5 years if taken by the eligible population with clinical ASCVD. Despite these encouraging results, ezetimibe would not be considered cost-effective ($154,000 per QALY) at the average annual cost of $2878.[40] Models estimate that ezetimibe would only be cost-effective beyond an 80% reduction of the brand price.[41] Generic ezetimibe was approved by the US Food and Drug Administration in December 2016, and dedicated cost-effectiveness studies of generic ezetimibe are warranted.

Similarly, PCSK9 inhibitors are not considered cost-effective at the current listed price of about $14,000 per year.[40,42,43] Models of US practice data (eg, insurance claims) have a higher baseline risk and thus more favorable cost-effectiveness compared with trial-based models.[43] Studies that include revascularization outcomes also have more favorable cost-effectiveness.[42,43] Despite these differences, models agree that to achieve thresholds of $100,000 per QALY or $150,000 per QALY, price reductions are needed below ranges of $4215 to $5459 per year and $6780 to $9669 per year, respectively.[42-44] Of note, pharmaceutical companies and health care systems in the United States have likely negotiated prices that are considerably lower than the listed price for PCSK9 inhibitors, although those figures are not publicly disclosed.

This discussion extends into the larger-scale debate over the price of drug therapies in the United States relative to other countries. In the United Kingdom, for instance, evolocumab is listed for less than 50% of the US price.[45] A more practical approach to reduce the budget impact of PCSK9 inhibitors and improve cost-effectiveness is to concentrate its use in the highest-risk groups most likely to achieve substantial benefit (eg, patients with multivessel CHD, those with more recent or multiple MIs, PAD).

GUIDELINE RECOMMENDATIONS FOR STATIN AND NONSTATIN THERAPIES

The most recent iteration of guidelines for lipid therapies and prevention of CV events are summarized in the Table. Overall, several recommendations are similar among these guidelines. First, there is an emphasis on the importance of healthy lifestyle habits for lipid-lowering effects and global CV health. As a side note, the rate of adherence to lifestyle changes at a population level remains disappointing. The AHA's definition of ideal CV health composes Life's Simple 7: not smoking, healthy diet, adequate physical activity, ideal body weight, and ideal blood pressure, glycemia, and cholesterol levels. Based on data from the 2011-2012 National Health and Nutrition Examination Survey, less than 20% of US adults meet 5 or more of Life's Simple 7.[50,51] Several strategies are available to improve lifestyle changes at an individual and populational level and are beyond the scope of this review.[51-54]

Second, plasma LDL-C levels are considered causal in atherosclerosis and as a result serve as therapeutic goals in patients who

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warrant LDL-C-lowering agents. Third, risk assessment is a key factor in selecting patients for pharmacological intervention in primary prevention. Fourth, statins are the mainstay of pharmacological therapy. Fifth, ezetimibe and PCSK9 inhibitors were added as potential agents for secondary prevention and for high-risk primary prevention patients who do not meet LDL-C targets despite lifestyle changes and adherence to maximally tolerated statin doses.

Several factors influence the decision between ezetimibe and PCSK9 inhibitors when additional LDL-C lowering is warranted, such as costs, route of administration, pill burden, and patient preferences. Health care professionals should also consider the degree of additional LDL-C lowering desired. Patients who require less than 25% additional lowering of LDL-C to attain an LDL-C level in the desirable range should do well with generic ezetimibe, but those with a history of ASCVD or high-risk primary prevention who require more than 25% LDL-C lowering to reach an LDL-C level of less than 50 mg/dL in addition to maximally tolerated statin therapy may need PCSK9 inhibition.

CONCLUSION

This is an exciting time for the field of lipid therapies and CV disease prevention. The pharmacological armamentarium for the treatment of dyslipidemias has expanded substantially in recent years. Ezetimibe and the PCSK9 inhibitors evolocumab and alirocumab have demonstrated improved clinical outcomes by means of reducing LDL-C levels beyond statin therapy. Although these therapies appear to be safe and highly effective in reducing LDL-C levels by approximately 20% and 60%, respectively, their costs warrant an important discussion about cost-effectiveness and appropriate patient selection for these drugs.

If we are to use these resources in a cost-conscientious manner, there are 3 fundamental principles to follow in the treatment of patients with elevated blood cholesterol levels. First, aggressive lifestyle changes are warranted in all patients to derive the highest possible benefit from nonpharmacological (and relatively inexpensive) interventions. Second, appropriate high-intensity generic statin therapy is currently underutilized and should be expanded to all patients meeting indications. Third, newer agents should be reserved for patients truly at highest risk of events. Whether that should include selected primary prevention patients, only those in need of secondary prevention, or even more strictly, only a higher-risk subset of the secondary prevention population (eg, those with PAD, recent or multiple previous MIs, multivessel CHD) will depend primarily on drug costs and on the longer-term follow-up of clinical trials, particularly mortality outcomes.

Abbreviations and Acronyms: **ACC/AHA** = American College of Cardiology/American Heart Association; **ASCVD** = atherosclerotic cardiovascular disease; **ARR** = absolute risk reduction; **CAC** = coronary artery calcium; **CHD** = coronary heart disease; **CV** = cardiovascular; **LDL-C** = low-density lipoprotein cholesterol; **MI** = myocardial infarction; **PAD** = peripheral arterial disease; **PCE** = Pooled Cohort Equations; **PCSK9** = proprotein convertase subtilisin/kexin type 9; **QALY** = quality-adjusted life-year

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