Statin guidelines made simple

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LDL Result During Study Year	Statin Intensity	n (% of Total)
<50 mg/dL	Low	97 (2.6)
	Moderate	18 (0.5)
	Subtotal	115 (3.0)
50 to 69 mg/dL	Low	307 (8.1)
	Moderate	51 (1.4)
	Subtotal	358 (9.5)
70 to 99 mg/dL	None	2349 (62.3)
	Low	854 (22.6)
	Moderate	96 (2.5)
	Subtotal	3299 (87.5)

ACC/AHA indicates American College of Cardiology/American Heart Association 2013 Cholesterol Guidelines; ATP III, National Cholesterol Education Program Adult Treatment Panel 2001 Cholesterol Guidelines; LDL, low-density lipoprotein.

Table 2
Statin Classification by Expected LDL-C Reduction (2013 ACC/AHA Guideline)

High-Intensity Therapy[a]	Moderate-Intensity Therapy[b]	Low-Intensity Therapy[c]
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg

[a] Expected LDL reduction: ≥50%.
[b] Expected LDL reduction: ≥30% to <50%.
[c] Expected LDL reduction: <30%.
ACC/AHA: American College of Cardiology/American Heart Association; -C: cholesterol; XL: extended-release.
Source: Reference 20.

Table. A Trial-Based Approach to Statin Guidelines

Patient Group	Major Supporting Trials
Secondary prevention	
High-quality randomized clinical trial data support the use of statin therapy as an effective adjunct to diet, exercise, and smoking cessation for secondary prevention patients with a history of myocardial infarction, stroke, or clinically apparent atherosclerosis	4S, CARE, LIPID, PROSPER, HPS
High-quality randomized clinical trial data in secondary prevention support maximizing the intensity of statin treatment and maintaining compliance with the treatment regimen	PROVE-IT, TNT, IDEAL, A to Z, SEARCH
Primary prevention	
High-quality randomized clinical trial data support the use of statin therapy as an effective adjunct to diet, exercise, and smoking cessation in the setting of primary prevention for middle-aged and older individuals with elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, elevated C-reactive protein, or multiple risk factors inclusive of diabetes and hypertension	WOSCOPS, MEGA, AFCAPS/TexCAPS, CARDS, ASCOT-LLA, JUPITER
Heart failure and renal insufficiency	
High-quality randomized clinical trial data do not support the use of statin monotherapy for adults with isolated heart failure or those undergoing hemodialysis	CORONA, GISSI-HF, 4-D, AURORA
High-quality randomized clinical trial data support the use of statin therapy among adults with chronic renal insufficiency, at least when given in combination with ezetimibe	SHARP
Other conditions	
For adults who do not meet the above criteria, physicians may consider issues such as genetic predisposition or a strong family history of premature coronary disease when making decisions for individual patients; For some patients, such as those suspected of having familial hyperlipidemia, referral to lipid or atherosclerosis specialists may be useful for consideration of further evaluation and the use of statins despite the absence of hard end point trial data	None—clinical judgment, expert opinion

Table 2
Statin medications by dose and treatment intensity

Intensity class	LDL cholesterol effect	Drug, dosage	Notes
Low	<30% reduction	Simvastatin, 10 mg Pravastatin, 10 to 20 mg Lovastatin, 20 mg Fluvastatin, 20 to 40 mg Pitavastatin, 1 mg	Lower potency is generally better tolerated with fewer side effects
Medium	30% to 50% reduction	Atorvastatin, 10 mg Rosuvastatin, 5 to 10 mg Simvastatin, 20 to 40 mg Pravastatin, 40 to 80 mg Lovastatin, 40 mg bid Pitavastatin, 2 to 4 mg	
High	>50% reduction	Atorvastatin, 40 to 80 mg Rosuvastatin, 20 to 40 mg	Higher potency may have more side effects, may be dosed regardless of time of day

LDL: low-density lipoprotein

Age	ASCVD	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • If LDL cholesterol ≥70 mg/dL (3.9 mmol/L) despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • If LDL cholesterol ≥70 mg/dL (3.9 mmol/L) despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

**In addition to lifestyle therapy. ^For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used. †Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, CKD, albuminuria, and family history of premature ASCVD. ‡High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. #Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of nonstatin-based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.*

The U.S. Department of Veterans Affairs and Department of Defense (VA/DoD), a health system with more than 20 million beneficiaries, has developed clinical practice guidelines over the past 25 years to promote straightforward, evidence-based care. In June 2020, the third iteration of the VA/DoD guidelines on managing dyslipidemia was published1 (see Figure 1 in the related practice guideline in this issue of American Family Physician). As members of the guideline working group, we believe that these recommendations create a simple, pragmatic, evidence-based approach that can be valuable to family physicians. Several of these guideline recommendations differ from those of the American College of Cardiology/American Heart Association (ACC/AHA; Table 1 and Table 2).1,2 In primary prevention, we recommend making treatment decisions based on clinical risk calculation, similar to the ACC/AHA. Cardiovascular disease risk calculators, such as the pooled cohort equations (, have reasonable accuracy to guide clinical decision-making.3 Other than the conventional risk factors included in calculators, no additional factors improve risk estimation.3 Coronary artery calcium scoring has not been demonstrated to improve patient outcomes, even in intermediate-risk populations where treatment decisions are less certain.3,4 Strong evidence supports moderate-dose statins as the best therapy in primary prevention for patients at elevated risk, with relative risk reductions in cardiovascular events and mortality of 20% to 30% over five years.5 Moderate-dose statins are well tolerated, with minimal risk of diabetes mellitus or rhabdomyolysis.6 Limited study of high-dose statins for primary prevention shows similar cardiovascular benefits as moderate-dose statins, with increased risks of diabetes and statin intolerance.7 Ezetimibe (Zetia) has not been studied as monotherapy and, in combination with a statin, is not better than statins alone.8 Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have not been shown to reduce risk better than placebo in primary prevention.9 Icosapent ethyl was not beneficial in the primary prevention subgroup of a randomized trial.10 The ACC/AHA guidelines also recommend moderate-dose statins, although high-dose statins and additional medications are suggested for certain conditions despite lack of evidence of superior outcomes.2 These suggestions are extrapolated from a goal of at least 50% low-density lipoprotein cholesterol (LDL-C) reduction, which is supported by observational data but not by direct clinical trials.2 Because primary prevention trials did not use risk calculators for inclusion criteria, treatment thresholds are somewhat arbitrary. The 7.5% ACC/AHA treatment threshold is based on an average of control group event rates in primary prevention trials.2 We recommend statin treatment at a 12% 10-year risk in patients with diabetes and in those with LDL-C levels of 190 mg per dL (4.92 mmol per L) or greater to most closely correspond to the clinical trial populations.1 The ACC/AHA similarly recommends treatment in patients who have diabetes and who have LDL-C levels of 190 mg per dL or greater.2 We recommend shared decision-making for treatment between 6% and 12% risk because few trials included patients in this risk category.1 We recommend against medication treatment in people with a 10-year risk less than 6% because evidence is lacking for this group.1 For secondary prevention, we recommend moderate-dose statins as the mainstay of treatment. This is consistent with trial evidence, and evidence is insufficient to show improved cardiovascular and all-cause mortality with higher-intensity treatment over moderate-dose statins.11 Moderate-dose statins have fewer adverse effects than high-dose statins; therefore, we strongly recommend them as the first step in therapy to reduce cardiovascular risk.1,6 The ACC/AHA recommends intensive therapy in secondary prevention unless medications cannot be tolerated.2 We recommend offering more intensive therapy to patients who wish to further reduce their risk.1 Switching to high-dose statins and adding ezetimibe or PCSK9 inhibitors to statins reduces nonfatal cardiovascular events more than moderate-dose statins alone, each to a similar extent.11 All were studied primarily in higher-risk populations, such as those with acute coronary syndrome, recurrent cardiac events, or tobacco use. Because of the uncertain long-term effects and high cost of PCSK9 inhibitors, we recommend increasing the statin dose and adding ezetimibe before considering the use of PCSK9 inhibitors.1 Icosapent ethyl reduced cardiovascular morbidity and mortality in a single randomized trial among secondary prevention patients with elevated triglyceride levels.2 The high rates of events in the control group and lack of corroborating studies limit our confidence in recommending this medication. Although the ACC/AHA recommends treating to LDL-C targets, this paradigm has not been prospectively studied.1,2 All primary and secondary prevention trials compared medication doses, most often a medication compared with placebo. Although post-hoc meta-analyses show that higher-intensity medications correlate with lower LDL-C levels and lower event rates, these secondary analyses do not add any specificity to existing trial results.12 We recommend treatment based on medication intensity to match the evidence, which also simplifies monitoring. After starting medication based on treatment intensity, further measurement of cholesterol is unnecessary. Even while making primary prevention decisions, we find the evidence supports infrequent lipid monitoring. Risk calculators demonstrate that patient factors such as obesity, hypertension, diabetes, and tobacco use influence risk scores significantly more than cholesterol values. Cholesterol levels are stable for up to 10 years, with most change between measurements due to testing variability.13 There is no need to repeatedly measure cholesterol more than once a decade for risk calculations. Using previous cholesterol values to calculate risk every two to five years offers the opportunity to decrease unnecessary testing. When cholesterol levels are measured, nonfasting samples have equivalent accuracy and should be used routinely. Indications for fasting samples are limited, such as verifying hypertriglyceridemia if considering icosapent ethyl. Editor's Note: Dr. Arnold is a contributing editor for American Family Physician. The views expressed in this article are those of the authors and do not reflect the position of the Department of the Navy, Uniformed Services University of the Health Sciences, Department of Defense, Department of Veterans Affairs, or the U.S. government. The enormous importance of cholesterol management for reduction and prevention of atherosclerotic cardiovascular disease (ASCVD) cannot be overstated.While ample evidence exists that reductions in low-density lipoprotein cholesterol (LDL-C) reduce the risk of cardiovascular events and death in patients with ASCVD, data gathered by the American College of Cardiology (ACC) from the PINNACLE registry reveal that 21.1% of these patients had no history of lipid-lowering therapy use and 84.5% did not meet LDL-C goal of less than 70mg/dL.1 Patients with ASCVD least likely to achieve LDL-C goals while on a statin include younger patients, African Americans, and hypertensive patients.1 These facts underscore the importance of determining and overcoming barriers to achieving optimal cholesterol management.Timothy Attebery, DSc, MBA, FACHE, Chief Executive Officer of the American College of Cardiologists states, “Management of lipid disorders has become more complex as new data, drugs and clinical standards around lipid management are introduced. The College has many successful tools and initiatives that have helped our members provide the most advanced and effective lipid management strategies for their patients, but there is more work to be done.”2 In 2019, the American College of Cardiology in cooperation with the American Heart Association (AHA) issued updated guidelines, made simple, for management of blood cholesterol. In these guidelines they highlight ten take-home messages to reduce the risk of ASCVD through cholesterol management.3 Clinicians should always emphasize a heart-healthy lifestyle throughout life with particular focus on avoidance of developing the metabolic syndrome.High-intensity statin therapy (if tolerated) should be instituted in patients with clinical ASCVD with the goal of lowering LDL-C levels by greater than or equal to 50%.Consider adding a non-statin cholesterol lowering agent (such as ezetimibe) in very high-risk ASCVD with a LDL-C threshold of 70mg/dL.Clinicians should begin high-intensity statin therapy in patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]).Moderate intensity statin therapy should be instituted in patients 40-75 years of age with diabetes mellitus and LDL-C levels greater than 70mg/dL.Clinicians should have a discussion with their patients about primary ASCVD prevention before starting statin therapy.Moderate-intensity statin therapy should be considered in non-diabetic adults 40-75 and LDL-C levels greater than 70mg/dL.Statin therapy should be considered in non-diabetic adults with a 10-year risk of 7.5% to 19.9%.If a decision about statin therapy is uncertain in Non-diabetic adults with LDL-C levels greater than 70mg/dl to 189 mg/dL and a 10-year risk for ASCVD of greater than 7.5%-19.9% a Coronary Artery Calcium (CAC) Score should be calculated to aid in the decision.Four to twelve weeks after statin initiation clinicians should assess adherence and percentage response to LDL -C lowering medications and lifestyle changes with repeat LDL levels and then every 3 to 12 months as needed.These guidelines are concise and should be easily attainable with the tools we possess. However, being armed with a primer for good care clearly is not enough. The American College of Cardiology in conjunction with Sanofi and Regeneron Pharmaceuticals Inc. have developed an initiative called the TRANSFORM LDL-C trial aimed at addressing the gaps in treatment for ASCVD patients with regards to cholesterol-lowering therapy. Dharam Kumbhani, MD, SM, FACC is a senior author of the TRANSFORM LDL-C trial. Dr. Kumbhani states, “Large groups of patients with ASCVD are not achieving low enough LDL-C levels, which puts them at greater risk of recurrent cardiovascular events and death.”1 The TRANSFORM LDL-C initiative aims to optimize patients’ access to the latest evidence-based treatments for LDL-C lowering and cardiovascular event risk reduction based on the ACC/AHA guidelines.1 Dr. Kumbhani goes on to say, “It’s apparent that large gaps exist and that more efforts are needed in implementing the cholesterol guidelines. Next steps are examining what barriers exist in achieving these treatment goals and how to address these barriers.” These barriers, once identified, will need to be addressed if the gaps in treatment, access, and goal achievement are to be eliminated.In general, before the results of the TRANSFORM LDL-C initiative are known, things can be done to reduce barriers to achieving the recommended LDL-C targets in patients with ASCVD. Simplifying treatment regimens can increase adherence especially in patients with several comorbidities such as hypertension and hyperlipidemia. Prescribing single-pill combinations containing treatment for both conditions makes it more likely the patient will comply with their regimen.4 Further, initiating treatment early with regular follow up and positive reinforcement from clinicians at each office visit are a good first step toward reducing cardiovascular risk in patients with hyperlipidemia. Together we can take the evidence and guidelines at our disposal and eliminate barriers to achieving the results our patients deserve improving outcomes and the quality of their lives.