High-Intensity Statins Benefit High-Risk Patients: Why and How to Do Better

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Abstract

Review of the US and European literature indicates that most patients at high risk for atherosclerotic cardiovascular disease (ASCVD) are not treated with high-intensity statins, despite strong clinical-trial evidence of maximal statin benefit. High-intensity statins are recommended for 2 categories of patients: those with ASCVD (secondary prevention) and high-risk patients without clinical ASCVD. Most patients with ASCVD are candidates for high-intensity statins, with a goal for low-density lipoprotein cholesterol reduction of 50% or greater. A subgroup of patients with ASCVD are at very high risk and can benefit by the addition of nonstatin drugs (ezetimibe with or without bile acid sequestrant or bempedoic acid and/or a proprotein convertase subtilisin/kexin type 9 inhibitor). High-risk primary prevention patients are those with severe hypercholesterolemia, diabetes with associated risk factors, and patients aged 40 to 75 years with a 10-year risk for ASCVD of 20% or greater. In patients with a 10-year risk of 7.5% to less than 20%, coronary artery calcium scoring is an option; if the coronary artery calcium score is 300 or more Agatston units, the patient can be up-classified to high risk. If high-intensity statin treatment is not tolerated in high-risk patients, a reasonable approach is to combine a moderate-intensity statin with ezetimibe. In very high-risk patients, proprotein convertase subtilisin/kexin type 9 inhibitors lower low-density lipoprotein cholesterol levels substantially and hence reduce risk as well.

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consensus recommendation identifies types of patients for whom intensive statin therapy is needed.

Two categories of patients are candidates for high-intensity statins: those with clinical ASCVD (secondary prevention) and high-risk patients without clinical ASCVD (high-risk primary prevention) (Figure). Clinical ASCVD includes acute coronary syndrome, history of myocardial infarction, stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease including aortic aneurysm, all of atherosclerotic origin.

**Secondary prevention of ASCVD**
Clinical ASCVD includes acute coronary syndrome, history of myocardial infarction, stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease including aortic aneurysm, all of atherosclerotic origin.

**Primary prevention of ASCVD**
Groups that benefit from high-intensity statin therapy
- Severe primary LDL-C ≥ 190 mg/dL (4.9 mmol/L), especially those with FH
- Diabetes: Age 40-75 y with 10-y ASCVD risk ≥ 7.5% with high-risk DM features*
- Primary prevention: Age 40-75 y with 10-y ASCVD risk ≥ 20% if measured, a coronary artery calcium score ≥ 300 Agatston units**

**Therapeutic options for high-risk patients**
- High-intensity statin first-line therapy
- Ezetimibe second-line option: combine with moderate-intensity statin
- PCSK9 inhibitor option for ASCVD patients or FH patients who either cannot take statins or have inadequate LDL-C lowering based on their risk***

**FIGURE.** Candidates for high-intensity statins. *High-risk diabetes mellitus (DM) features include long duration (type 2, ≥ 10 years; type 1, ≥ 20 years), albuminuria (≥ 30 mg of albumin per mg of creatinine), estimated glomerular filtration rate less than 60 mL/min per 1.73 m², retinopathy, neuropathy, ankle-brachial index less than 0.9. **If obtained in patients with intermediate (7.5% to 19.9%) 10-year atherosclerotic cardiovascular disease (ASCVD) risk in whom a risk decision regarding statin use is uncertain. A lipid specialist may be helpful for these patients.*** **FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.**

**HIGH-RISK PATIENTS OFTEN NOT TREATED WITH HIGH-INTENSITY STATINS**
In the United States and Europe, most high-risk patients are not treated with high-intensity statins.8-14 For example, Rosenson et al9 reported that among Medicare beneficiaries with coronary heart disease events, most do not fill high-intensity statin prescriptions after hospitalization. After discharge, statin therapy is progressively discontinued.13 Even in RCTs, statin usage declines over the course of the study. A decline in usage is also observed in large registry databases.13

Statin discontinuation relates to (1) the health care system (access to medical care, multiple clinicians, high cost of insurance coverage and drug costs in some cases), (2) the clinical team (eg, discharge counseling and/or failure to prescribe high-intensity...
Statin-associated adverse effects are commonly blamed for failure to use high-intensity statins. Symptoms may be related to extraneous conditions, anticipated adverse effects (nocebo phenomenon), or true somatic involvement. Myalgias (statin-associated muscle symptoms) are the most common. The reported frequencies of statin-associated muscle symptoms in outpatients range from 5% to 20%. Marked elevations of creatine kinase, which are indicative of muscle injury, are rare. The possibility that statin-associated muscle symptoms reflect muscle involvement is suggested because severe myopathy (rhabdomyolysis) can occur, albeit rarely. Severe myopathy occurs most commonly from excessive systemic exposure to statins; normally, statins are rapidly removed by the liver, and blood levels are kept very low. A rise in blood levels of statins can occur if their metabolism is impaired. High-intensity statins can raise blood levels more than moderate-intensity statins and thus make statin-associated muscle symptoms more likely. Other factors predisposing patients to statin myopathy are frailty in elderly patients, Asian ancestry, repetitive muscular traumas, excess alcohol intake, untreated hypothyroidism, or untreated vitamin D deficiency. Drugs that impair statin metabolism, such as gemfibrozil, should be avoided. Less well-known interactions can be determined by use of drug interaction checkers that are widely available electronically or by consultation with a pharmacist. Red yeast rice is a supplement that contains a statin similar to prescription lovastatin and should be discontinued in patients receiving statin therapy. Severe myopathy in statin users should not be confused with the extremely rare occurrence of statin-induced autoimmune myopathy, which can persist after discontinuing statin therapy.

HIGH-INTENSITY STATINS GENERALLY WELL TOLERATED

Musculoskeletal pain is common in adults aged 40 years or older without arthritis, often making the evaluation of myalgias challenging. In clinical trials in which patients with statin-associated muscle symptoms undergo a washout period and are then given either placebo or a statin, a significant number (30% to 40%) have no symptoms on statin rechallenge. Thus, a dechallenge-rechallenge strategy as suggested by the AHA/ACC/MS cholesterol guideline is reasonable. The 2 high-intensity statins are atorvastatin at 40/80 mg/d and rosuvastatin at 20/40 mg/d. In clinical trials comparing atorvastatin at 80 mg/d with 3 moderate-intensity statins (atorvastatin at 10 mg/d, simvastatin at 20/40 mg/d, or pravastatin at 40 mg/d), high-intensity atorvastatin was tolerated similarly to moderate-intensity atorvastatin. In a recent RCT, muscle symptoms were found to be independent of atorvastatin dosage. In the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) study, high-intensity rosuvastatin at 20 mg/d was compared with placebo; adverse effects attributable to rosuvastatin were infrequent. Thus, the view that moderate-intensity statins are better tolerated overall than high-intensity statins is not supported by RCTs.

Some investigators advocate initiating statin therapy with a moderate-intensity agent and, if well-tolerated, up-titrating to a higher dose. However, because most patients tolerate a high-intensity statin, there is no compelling reason other than patient preference to start with a low- to moderate-intensity statin followed by up titration. If a patient who has begun taking a high-intensity statin convincingly demonstrates statin-associated adverse effects, however, a moderate-intensity statin should be tried. Nevertheless, any decision about lowering the statin dose should be made in the context of the clinician-patient risk discussion. This decision must be made with
the understanding that a portion of the statin benefit will be lost unless offset by combining ezetimibe with a moderate-intensity statin.

One concern about use of a high-intensity statin is the risk of new onset of diabetes. A meta-analysis indicated that a high-intensity statin was associated with a greater risk of new-onset diabetes than a moderate-intensity statin. Conversely, high-intensity statins are more beneficial for reducing ASCVD. In the JUPITER trial, new-onset diabetes occurred in 3% of those assigned rosuvastatin compared with 2.4% of those assigned to placebo (P=0.01). Despite this finding, reduction in vascular events far outweigh the development of new-onset diabetes. Nonetheless, if a clinician is concerned about development of new-onset diabetes in a patient with risk factors for diabetes (body mass index [calculated as weight in kilograms divided by height in meters squared] ≥30 kg/m², metabolic syndrome, fasting blood glucose ≥100 mg/dL [to convert to mmol/L, multiply by 0.0555], hemoglobin A₁c 6% to 6.4% [to convert to proportion of total hemoglobin, multiply by 0.01]) with high-intensity statin therapy, an alternative is to combine ezetimibe with a moderate-intensity statin. More importantly, avoidance of weight gain and emphasis on a healthy dietary pattern with daily moderate physical activity in patients already at risk for diabetes should be emphasized when statin therapy is initiated.

STRATEGIES IF HIGH-INTENSITY STATINS CANNOT BE USED

If, for whatever reason, a high-intensity statin is replaced by one of low or moderate intensity, adding a nonstatin drug can restore the LDL-C reduction. Available nonstatins are ezetimibe, bile acid sequestrants, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Ezetimibe is the most convenient replacement drug. A moderate-intensity statin plus ezetimibe produces LDL-C lowering similar to that of a high-intensity statin, generally 50% or greater. Importantly, the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study found that a moderate-intensity statin plus ezetimibe reduces ASCVD risk more than a moderate-intensity statin alone. That ezetimibe alone reduces ASCVD was recently confirmed in older Japanese patients. Moreover, if only a low-intensity statin can be tolerated, adding ezetimibe plus a bile acid sequestrant should lower LDL-C almost as much as a high-intensity statin. The use of PCSK9 inhibitors for patients with ASCVD is discussed subsequently in the section on secondary prevention.

The European Society of Cardiology/European Atherosclerosis Society dyslipidemia guidelines classify icosapent ethyl as a nonstatin agent that can be combined with statin therapy to enhance risk reduction. This omega-3 fatty acid is an ethyl ester of eicosapentaenoic acid. A recent RCT found icosapent ethyl to incrementally reduce ASCVD events by 25% in statin-treated patients with ASCVD, hypertriglyceridemia, and diabetes. The mechanism for benefit is currently under investigation, but apparently it is not due to lowering of LDL-C or triglyceride levels. Several RCTs of omega-3 fatty acids have had ambiguous results for benefit. Therefore, a second RCT testing of icosapent ethyl seems necessary to justify a class 1A recommendation for statin-treated patients.

A recently approved drug, bempedoic acid, lowers LDL-C in the range of 15% to 20% when combined with a maximally tolerated statin. Long-term safety and efficacy for bempedoic acid has not been proven in a randomized controlled outcomes trial; thus, at present the drug cannot be considered first-line therapy. However, the drug is currently being evaluated for cardiovascular disease risk reduction in statin-intolerant patients. The US Food and Drug Administration recently approved a combination of bempedoic acid at 180 mg and ezetimibe at 10 mg for high-risk patients. This combination is an option when ezetimibe alone is indicated and will obtain an approximate 38% lowering of LDL-C.
ROLE OF HIGH-INTENSITY STATINS IN SECONDARY PREVENTION

According to the AHA/ACC/MS guideline,6 the first goal in patients with ASCVD is to reduce LDL-C levels by 50% or more. In the United States, many clinicians believe that a reasonable LDL-C goal for patients with ASCVD is less than 70 mg/dL. This belief is based on previous recommendations from national organizations for patients who have ASCVD and multiple high-risk conditions.60,61 In treating very high-risk patients with ASCVD, the 2018 AHA/ACC/MS guideline6 specified an LDL-C threshold of 70 mg/dL for consideration of the addition of nonstatin therapy to a maximal-dose statin. This value implies an LDL-C goal of less than 70 mg/dL for patients at very high risk. However, for most patients with stable ASCVD who are not at very high risk, a 50% or greater reduction in LDL-C should be sufficient because percentage risk reduction increases with greater LDL-C levels.1,6 Moreover, because most patients will have a baseline LDL-C level of less than 140 mg/dL, they would be expected to have a decrease in LDL-C to less than 70 mg/dL while taking a high-intensity statin.5 Regardless, the addition of a nonstatin drug to maximal statin therapy is an option in high-risk patients with ASCVD.

The AHA/ACC/MS guideline6 recognized the efficacy of PCSK9 inhibitors when on-treatment LDL-C levels in very high-risk patients remain at 70 mg/dL or greater while they are receiving maximal statin therapy plus ezetimibe. The European Society of Cardiology/European Atherosclerosis Society dyslipidemia guidelines33 differ in that they specified dual goals for LDL-C for all patients with ASCVD: 50% or greater reduction and a goal of less than 55 mg/dL. The latter value opens the door to a still greater use of PCSK9 inhibitors, which challenges the cost-effectiveness of these drugs for many patients.

A minority of patients with ASCVD report repeated statin-associated adverse effects and cannot tolerate any dose of statins despite rechallenge or switching statins. In such patients, a PCSK9 inhibitor is a reasonable alternative for risk reduction. In patients with a history of statin-associated adverse effects, PCSK9 inhibitors are well tolerated and very efficacious for LDL-C lowering.62-66 The major question about PCSK9 inhibitors is their cost-effectiveness. As their cost declines, cost-effectiveness will improve.67,68

ROLE OF HIGH-INTENSITY STATINS IN HIGH-RISK PRIMARY PREVENTION

Patients with ASCVD generally have a 10-year risk for new cardiovascular events of 20% or greater.69 High-risk primary prevention, therefore, can be defined as a 10-year risk for new-onset ASCVD of 20% or more. In the 2018 AHA/ACC/MS guideline,9 this category encompasses (1) severe primary hypercholesterolemia (LDL-C ≥190 mg/dL), (2) diabetes with risk factors in middle age (40 to 75 years), and (3) 10-year risk of 20% or greater as estimated by the pooled cohort equations (PCE) without diabetes at age 40 to 75 years. We, along with some experts, favor high-intensity LDL-C lowering in patients with a 10-year ASCVD risk of 7.5% to less than 20% plus a CAC score of 300 or more Agatston units.

Severe primary hypercholesterolemia is defined as an LDL-C level of ≥190 mg/dL without secondary causes, such as excessive dietary saturated fat, trans fat, or cholesterol intake (as seen in some ketogenic diets, for example), hypothyroidism, nephrotic syndrome, or obstructive liver disease. In patients without secondary causes, a high-intensity statin is first-line therapy. This dose should reduce LDL-C levels by 50% or more. If a high-intensity statin cannot be tolerated, the combination of a moderate-intensity statin plus ezetimibe should achieve a similar LDL-C lowering. If further LDL-C reduction is needed, it may be reasonable to add a PCSK9 inhibitor70; referral to a lipid specialist can be helpful.

Diabetes in patients aged 40 to 75 years confers a high lifetime risk for ASCVD. Randomized controlled trials in patients with diabetes have tested only moderate-intensity statins. However, with advancing age and accumulation of multiple ASCVD risk factors or diabetes-specific
TABLE 1. Clinical Approach to Maximal LDL-C Lowering

<table>
<thead>
<tr>
<th>Approach</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Strive for maximum LDL-C lowering</td>
<td>High-intensity statins that achieve 50% or more LDL-C lowering can reduce risk for ASCVD by one-third more than moderate-intensity statins</td>
</tr>
<tr>
<td>2. Expect patients to tolerate statins</td>
<td>Approximately 90% of patients can tolerate high-intensity statins without substantial statin-associated adverse effects. Strategies are available if they do not</td>
</tr>
</tbody>
</table>
| 3. Control other risk factors                                          | Smoking cessation  
Control blood pressure  
Control blood glucose  
Avoid weight gain  
Weight reduction if metabolic syndrome is present                                                                                       |
| 4. Rule out and address secondary causes of hypercholesterolemia       | Examples include hypothyroidism, nephrotic syndrome, poor diet, uncontrolled diabetes, and medications                                                                                                      |
| 5. Understand high-intensity options                                   | If atorvastatin at 80 mg or rosuvastatin at 40 mg are not tolerated or acceptable, try atorvastatin at 40 mg or rosuvastatin at 20 mg to get approximately 50% lowering of LDL-C                                             |
| 6. Do not assume that statin-associated symptoms are due to the statin | In placebo-controlled studies, significant numbers of patients have been found to not have statin-related symptoms  
Careful questioning of patients as to location, timing, and other causes of pain may reveal the cause of current symptoms                                                                                   |
| 7. If statin-related symptoms occur; they usually abate with stopping the statin, so a lower dose or different statin can be given after a brief abstinence and resolution of symptoms | Bilateral proximal extremity (often lower) muscle pains, aches, or muscle fatigue that occurs within 1-2 wk and disappears promptly within 4-7 d of cessation of the statin suggests that the symptom is statin-related. After a brief abstinence and resolution of symptoms, rechallenge with a lower dose or alternative statin in a starting dose is appropriate. If symptoms persist—especially weakness—prompt evaluation is needed with physical examination, laboratory studies such as measurement of CK and sedimentation rate/CRP to rule out inflammation, and a lipid specialist consultation |
| 8. If only moderate-intensity statins are tolerated, add ezetimibe at 10 mg/d (± bile acid resin or bempedoic acid) to achieve further LDL-C lowering | Ezetimibe (± bile acid resin or bempedoic acid) is well tolerated and allows for achievement of 50% lowering of LDL-C when combined with a moderate-intensity statin                                                                 |
| 9. If similar symptoms recur with a second statin, try an alternative treatment strategy. For example: ezetimibe at 10 mg/d (± bile acid resin or bempedoic acid) with intermittent statin dosing can lower LDL-C substantially | Consider starting with ezetimibe at 10 mg/d (± bile acid resin or bempedoic acid) to provide positive reinforcement for persistent commitment to lowering LDL-C. Then add once-daily low-intensity statin or less than daily generic long-acting statins, such as rosuvastatin at 5 mg twice per week or atorvastatin at 10 mg 3 times per week. May achieve about 40% LDL-C lowering |
| 10. If patient is unable or unwilling to take statins, then consider an alternative strategy utilizing LDL-C—lowering drugs proven to reduce LDL-C and coronary events. PCSK9 inhibitors, possibly with ezetimibe, can be useful in such cases | Consider PCSK9 inhibitors in appropriate patients after cost/benefit discussion. Some patients may wish to try a vegan diet                                                                                     |

*ASCVD, atherosclerotic cardiovascular disease; CK, creatine kinase; CRP, C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9  
*bUS Food and Drug Administration approved, but long-term safety and clinical efficacy have not been documented in a randomized controlled trial for bempedoic acid.
A 10-year risk of 20% or more in adults aged 40 to 75 years without diabetes can be classified as high risk with PCE alone. These patients are candidates for high-intensity statin therapy, or if this intensity is not tolerated, a moderate-intensity statin

TABLE 2. Overcoming Common Barriers to Use of High-Intensity Statins in the Clinician-Patient Risk Discussion

<table>
<thead>
<tr>
<th>Barrier</th>
<th>How to address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle symptoms</td>
<td>RCTs report similar incidence with high- vs moderate-intensity statins. Employ systematic approach if muscle symptoms arise</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Slight increase in incidence Benefit of statin substantially outweighs risk</td>
</tr>
<tr>
<td>Indications to start with moderate-intensity statins</td>
<td>Greater risk reduction with high-intensity statins Avoid dosing inertia</td>
</tr>
<tr>
<td>Fear of drug interactions</td>
<td>Multiple tools available to minimize likelihood Pharmacy available to recheck</td>
</tr>
<tr>
<td>Concerns about polypharmacy</td>
<td>Remind patient that statins prevent MI and stroke and should be a priority among medications</td>
</tr>
<tr>
<td>Cost</td>
<td>Low-cost generic high-intensity statins are available</td>
</tr>
<tr>
<td>Patient understanding of why drug is needed</td>
<td>Emphasize MI and stroke risk reduction instead of just cholesterol reduction</td>
</tr>
<tr>
<td>Low education level</td>
<td>Employ patient-appropriate educational materials</td>
</tr>
<tr>
<td>Caregiver concerns</td>
<td>Simplicity of administration. Once a day</td>
</tr>
<tr>
<td>Need for repeated testing and follow-up</td>
<td>Reassure that once favorable results are achieved, once or twice a year may be adequate</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; RCT, randomized controlled trial.

TABLE 3. Patient Support Materials to Enhance Adherence to Evidence-Based Statin Therapy

<table>
<thead>
<tr>
<th>Organization</th>
<th>Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>American College of Cardiology</td>
<td>CardioSmart</td>
</tr>
<tr>
<td></td>
<td>Straight talk about statins</td>
</tr>
<tr>
<td></td>
<td><a href="https://www.cardiosmart.org/topics/high-cholesterol/treatment/straight-talk-about-statins">https://www.cardiosmart.org/topics/high-cholesterol/treatment/straight-talk-about-statins</a></td>
</tr>
<tr>
<td></td>
<td>Addressing side effects of statins</td>
</tr>
<tr>
<td>American Heart Association</td>
<td>Cholesterol medications</td>
</tr>
<tr>
<td>National Lipid Association</td>
<td>Patient and clinician tear sheets</td>
</tr>
<tr>
<td></td>
<td><a href="https://www.lipid.org/TearSheets">https://www.lipid.org/TearSheets</a></td>
</tr>
<tr>
<td>Preventive Cardiovascular Nurses Association</td>
<td>Tools for patients: patient education tools and handouts for your practice</td>
</tr>
<tr>
<td></td>
<td><a href="https://pcna.net/clinical-resources/patient-handouts/">https://pcna.net/clinical-resources/patient-handouts/</a></td>
</tr>
<tr>
<td>UpToDate</td>
<td>Rosenson RS, Cannon CP. Patient education: high cholesterol and lipid treatment options (Beyond the Basics). In: Freeman MW, Givens J, eds. UpToDate. 2021</td>
</tr>
<tr>
<td></td>
<td>Also local cardiac rehabilitation program may have good materials</td>
</tr>
</tbody>
</table>
can be combined with ezetimibe to obtain a 50% or greater reduction in LDL-C.

If a patient aged 40 to 75 years has a 10-year risk of 7.5% to less than 20% by PCE, measurement of CAC is an option that may, in selected individuals, affect the intensity of LDL-C therapy prescribed. Several authors71,72 contend that the presence of a CAC score of 300 or more Agatston units in a patient at intermediate risk favors use of a high-intensity statin. Such a patient has both multiple ASCVD risk factors and advanced subclinical atherosclerosis, which compounds risk.73

PRACTICAL TIPS FOR THE CLINICIAN-PATIENT DISCUSSION

Table 1 describes the strategy for use of maximal cholesterol-lowering therapy in high-risk patients, with emphasis on high-intensity statins. We acknowledge that there can be barriers to prescribing high-intensity statins in other than the acute coronary syndrome setting. Patients are concerned about a myriad of issues, including muscle-associated adverse effects, development of diabetes, polypharmacy, cost, and how frequently repeated testing will be required. Table 2 addresses these barriers along with tips for addressing the patient’s concerns. Clinicians also are concerned about a logical approach to the issue of high-intensity statins. In addition to shared decision making, which includes encouraging patients to ask questions, express values and preferences, and state their commitment to adhere to lifestyle changes and medications, many patients want additional materials to review. Table 3 provides links to trustworthy resources from several excellent organizations.

CONCLUSION

There is strong evidence that most patients at high risk for ASCVD benefit from substantial LDL-C lowering of 50% or more. Yet too often, such patients are unnecessarily undertreated with LDL-C—lowering therapy. Many reasons exist for undertreatment, but ultimately, in high-risk patients, the clinician needs to discuss the value of maximal LDL-C lowering and utilize regular monitoring for efficacy and adherence. Enhanced lowering can be achieved preferably by use of a high-intensity statin or if preferred, a moderate-intensity statin plus ezetimibe with or without a bile acid sequestrant, or bempedonic acid. For patients with ASCVD who are completely intolerant of statins, strong consideration should be given to use of a PCSK9 inhibitor.

Abbreviations and Acronyms: AHA/ACC/MS, American Heart Association/American College of Cardiology/multisociety; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; LDL-C, low-density lipoprotein cholesterol; PCE, pooled cohort equations; PCSK9, proprotein convertase subtilisin/kexin type 9; RCT, randomized controlled trial

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