Evolving Issues in Statin Selection

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INTRODUCTION
Statin therapy is the pharmacologic cornerstone for reducing low-density lipoprotein cholesterol (LDL-C) and preventing or slowing progression of atherosclerotic cardiovascular disease (ASCVD). Results from meta-analyses have indicated that statins reduce all-cause and cardiovascular (CV) mortality among patients with risk, including both primary and secondary populations. Statins also have an overall favorable safety profile, although numerous factors can negatively impact statin safety and tolerability.

Despite the overall safety and advances in ASCVD prevention with statin therapy, the primary care clinician is faced with optimally managing dyslipidemia among numerous patient populations. This is particularly true in primary prevention patients in which the initiation or intensity of statin therapy is uncertain. Others include those with metabolic syndrome (MetS) or patients on complex medication regimens who are prone to drug-drug interactions and statin-related adverse effects. To aid the clinician, the 2018 American College of Cardiology/American Heart Association Multisociety Guideline on the Management of Blood Cholesterol (2018 ACC/AHA Cholesterol Guideline) provides recommendations on appropriate statin selection and improved patient risk stratification. One such method to better risk stratify patients is the identification of factors that independently increase the risk of ASCVD, so-called risk-enhancing factors. These are supported by epidemiologic data indicating higher overall ASCVD risk and include common conditions such as chronic kidney disease (CKD), MetS, and chronic inflammatory conditions.

2018 ACC/AHA CHOLESTEROL GUIDELINES
Diabetes-specific risk enhancers
Diabetes mellitus has long been established as a major, independent risk factor for ASCVD, although the spectrum of CV risk can vary considerably. Clearly, a young patient newly diagnosed with type 1 diabetes mellitus (T1DM) has less CV risk compared to an older patient with longstanding type 2 DM (T2DM) and additional CV risk factors. A key guideline message specifically notes that among patients 40 to 75 years of age with DM and LDL-C ≥70 mg/dL (≥1.8 mmol/L), a moderate-intensity statin should be initiated without calculating 10-year ASCVD risk. Further, additional risk stratification may be necessary. Notably, the 2018 ACC/AHA Cholesterol Guidelines highlight important DM-specific risk-enhancers that increase ASCVD risk beyond DM and are independent of traditional CV risk factors. These are: (1) disease duration ≥20 years for T1DM and ≥10 years for T2DM; (2) albumin to creatinine ratio ≥30 mcg/mg; (3) estimated glomerular filtration rate <60 mL/min/1.73 m²; (4) retinopathy; (5) neuropathy; and (6) ankle-brachial index <0.9. Evaluating the patient for duration of DM and the presence of common long-term complications associated with DM will provide further risk stratification and help determine intensity of treatment.

Metabolic syndrome—impact on individualizing therapy
MetS is a clustering of conditions that markedly increases the risk of ASCVD, DM, and all-cause mortality (TABLE 1). Thereby, MetS is a risk-enhancing factor for ASCVD. Insulin resistance is considered an underlying cause of MetS and is strongly associated with prediabetes, DM, obesity, visceral adiposity, nonalcoholic steatohepatitis, and systemic inflammation. Rates of MetS closely parallel those of obesity in the United States, having increased dramatically in the past few decades. Currently, the prevalence of MetS is approximately one-third of US adults, although this may be an underestimation given insufficient screening rates.

MetS is also closely linked with other conditions including autoimmune diseases (eg, systemic lupus erythematosus, rheumatoid arthritis), CKD, and human immunodeficiency...
risk of an ASCVD event, the presence of risk-enhancing factors indicates greater risk. In this scenario, it is recommended to acknowledge the risk-enhancing factors and engage in a clinician-patient discussion to reduce CV risk through lifestyle management and possible initiation or intensification of statin therapy.1

Risk-enhancing factors that have been identified primarily from epidemiologic data elevate ASCVD risk by varying levels. The degree of lifetime risk is typically proportional to the magnitude of the risk-enhancing factor. For example, patients with vs without MetS have a relative risk (RR) for CV events of 1.78, while patients with both MetS and DM have a RR of 2.35.9,10 Similar data reported with chronic inflammatory conditions show the RR for major cardiometabolic diseases is 1.25 for psoriasis, 1.7 for rheumatoid arthritis and 6.4 for systemic lupus erythematosus.11 Finally, CV mortality follows the progression of CKD. The RR for CV events is 1.38 in patients with an estimated glomerular filtration rate (eGFR) of 45-59 mL/min/1.73 m² compared to 3.29 for an eGFR of 15-29 mL/min/1.73 m².12 Other notable conditions and RR for CV events include early menopause (1.32),13 a history of preeclampsia/eclampsia (2.28),14 and a family history of premature ASCVD (~2-fold),15 while the presence of HIV is associated with a nearly 3-fold increase in coronary heart

**TABLE 1** General risk-enhancing factors for additional risk stratification1

<table>
<thead>
<tr>
<th>Risk-enhancing factor</th>
<th>Description</th>
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<tbody>
<tr>
<td>Family history of premature ASCVD</td>
<td>(males, age &lt;55 years; females, age &lt;65 years)</td>
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<tr>
<td>Primary hypercholesterolemia (LDL-C 160-189 mg/dL; non-HDL 190-219 mg/dL)*</td>
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<tr>
<td>Metabolic syndrome (increased waist circumference, elevated triglycerides [≥150 mg/dL], elevated blood pressure, elevated fasting blood glucose, and low HDL-C [&lt;40 mg/dL in men; &lt;50 mg/dL in women] are factors; tally of 3 makes the diagnosis)</td>
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<tr>
<td>Chronic kidney disease (eGFR 15-59 mL/min/1.73 m², with or without albuminuria; not treated with dialysis or kidney transplant)</td>
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<td>Chronic inflammatory conditions such as psoriasis, RA, HIV/AIDS</td>
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<tr>
<td>History of premature menopause (before age 40 years) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia</td>
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<tr>
<td>High-risk race/ethnicities (eg, South Asian ancestry)</td>
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<tr>
<td>Lipid/biomarkers: associated with increased ASVCD risk</td>
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<tr>
<td>Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL)</td>
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<tr>
<td>If measured:</td>
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<tr>
<td>Elevated high-sensitivity C-reactive protein (≥2.0 mg/L)</td>
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<tr>
<td>Elevated Lp(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL constitutes a risk-enhancing factor especially at higher levels of Lp(a)</td>
<td></td>
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<tr>
<td>Elevated apolipoprotein B ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C &gt;160 mg/dL and constitutes a risk-enhancing factor</td>
<td></td>
</tr>
<tr>
<td>Ankle-brachial index &lt;0.9</td>
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</table>

Abbreviations: AIDS, acquired immunodeficiency syndrome; ASCVD, atherosclerotic cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; RA, rheumatoid arthritis.

*Optimally, 3 determinations.

The ASCVD risk estimator is a robust tool that predicts necessary to enhance ASVCD risk estimates and guide therapy. 

9 inhibitors) may be considered when LDL-C is ≥70 mg/dL to lower LDL-C by ≥50%. The addition of non-statin therapies important of a high-intensity or maximally tolerated statin those with ASCVD or severe hypercholesterolemia and the lifestyle across the life course. The next 3 messages focus on 

mate/). However, further risk stratification is often neces-


can identify 10-year risk (http://tools. acc.org/ASCVD-Risk-Estimator-Plus/#/calculate/esti-


disease.16 These findings stress the importance of a comprehen-
sive patient evaluation and incorporating risk-enhancing factors into clinical practice.

**Top 10 take-home messages**

An important section of the 2018 ACC/AHA Cholesterol Guidelines is a summary of 10 major take-home messages to reduce the risk of ASCVD through cholesterol management (TABLE 2).1 The first message emphasizes a heart healthy lifestyle across the life course. The next 3 messages focus on those with ASCVD or severe hypercholesterolemia and the importance of a high-intensity or maximally tolerated statin to lower LDL-C by ≥50%. The addition of non-statin therapies (eg, ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors) may be considered when LDL-C is ≥70 mg/dL in very high-risk patients or those with high baseline LDL-C. Another major point is that for most patients with DM, a moderate-intensity statin is appropriate unless multiple risk factors are present, in which case a high-intensity statin can be implemented to reduce LDL-C by ≥50%.

The remaining take-home messages involve patients for primary prevention and illustrate populations where clinicians often struggle to accurately identify ASCVD risk and the appropriate therapy. Tools such as the ACC/AHA ASCVD risk estimator can identify 10-year risk (http://tools. acc.org/ASCVD-Risk-Estimator-Plus/#/calculate/estimate/). However, further risk stratification is often necessary to enhance ASVCD risk estimates and guide therapy. The ASCVD risk estimator is a robust tool that predicts population risk, but is limited when estimating individual risk. Conversely, identifying risk-enhancing factors (TABLE 1) can influence individual risk, and confirms a higher risk state. The final take-home message is to assess adherence to lifestyle/medications and optimal percentage response for LDL-C goal achievements in 4 to 12 weeks, then every 3 to 12 months as needed.

**CONTRIBUTION OF STATIN THERAPY TO DIABETES MELLITUS**

**New-onset vs newly diagnosed**

In 2012, the US Food and Drug Administration (FDA) released a statement indicating an association with statin therapy and reports of increased glycated hemoglobin (A1c) and fasting serum glucose.17 That same year, the European Medicines Agency (EMA) reported an increased risk of new onset diabetes (NOD) in patients already at risk for DM and receiving statin therapy.18 Multiple studies have since confirmed this relationship and provided additional data to guide practice.

Screening patients to determine baseline glycemic values is recommended prior to initiating a statin.19 This is particularly important among patients at risk for DM, such as those with MetS since, if baseline values are not established and glucose elevations are observed poststatin initiation, the patient and practitioner may inherently assume the impaired values are statin-related. Screening is further supported by population data, as approximately 25% of US adults with T2DM and 90% of those with prediabetes are not aware of their glucose impairment.20, 21

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**Abbreviations:** ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol.


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**TABLE 2** Key take-home messages to reduce ASCVD through cholesterol management

<table>
<thead>
<tr>
<th>Message</th>
<th>Details</th>
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<tbody>
<tr>
<td>1.</td>
<td>In all individuals, emphasize a heart-healthy lifestyle across the life course.</td>
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<tr>
<td>2.</td>
<td>In patients with clinical ASCVD, reduce LDL-C with high-intensity statin therapy or maximally tolerated statin therapy.</td>
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<tr>
<td>3.</td>
<td>In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL to consider addition of nonstatins to statin therapy.</td>
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<tr>
<td>4.</td>
<td>In patients with severe primary hypercholesterolemia (LDL-C ≥190 mg/dL), without calculating 10-year ASCVD risk, begin high-intensity statin therapy.</td>
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<tr>
<td>5.</td>
<td>In patients 40 to 75 years of age with DM and LDL-C ≥70 mg/dL, start moderate-intensity statin therapy without calculating 10-year ASCVD risk.</td>
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<tr>
<td>6.</td>
<td>In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician-patient risk discussion before starting statin therapy.</td>
</tr>
<tr>
<td>7.</td>
<td>In adults 40 to 75 years of age without DM and with LDL-C levels ≥70 mg/dL, at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.</td>
</tr>
<tr>
<td>8.</td>
<td>In adults 40 to 75 years of age without DM and 10-year risk of 7.5% to 19.9%, risk-enhancing factors favor initiation of statin therapy.</td>
</tr>
<tr>
<td>9.</td>
<td>In adults 40 to 75 years of age without DM and with LDL-C ≥70 mg/dL to 189 mg/dL, at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.</td>
</tr>
<tr>
<td>10.</td>
<td>Assess adherence and percentage response to LDL-C-lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.</td>
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</table>
Statin-associated diabetes mellitus via unclear mechanism(s)

A host of mechanisms have been proposed to explain the association between statin therapy and NOD. Those discussed most commonly include decreased glucose transporter 4 (GLUT 4) expression, diminished levels of coenzyme Q10 (CoQ10), blocking calcium channels in pancreatic β cells, altering adiponectin concentrations, and single nucleotide polymorphisms (SNPs) resulting in inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR). Genetic analyses have also demonstrated certain HMGCR SNPs are associated with glucose impairment. Overall, the mechanism(s) responsible for the dysglycemic effects of statins are likely multifactorial, and vary among individual statins.

Modest increase in risk and populations more likely affected

The overall increase in NOD with statin therapy is generally considered to be modest, but data are mixed. Numerous studies have also been performed identifying the associated risk factors. Individuals with multiple features of MetS may be more prone to developing NOD with statin use. Other potential risk factors include female gender, older adults (~65-75 years), Asian ethnicity, extended duration of statin use, and those with a family history of DM.

In 2010, a meta-analysis was performed of 13 major randomized controlled trials (RCTs) comparing statin or placebo and incident DM. Overall, a 9% increased risk for incident DM was noted with statin therapy. This study, and other similar analyses, concluded that statin therapy is associated with a small but significant risk of NOD. Conversely, a 2015 meta-analysis of observational studies demonstrated a stronger association of statin therapy with NOD (RR, 1.44; 95% confidence interval [CI], 1.31-1.58) than that observed from RCT data. The authors of the meta-analysis emphasized rigorous monitoring for NOD with those prescribed statins, especially among patients with risk factors for DM. Limitations of the meta-analysis based on RCTs include a short follow-up period, underpowered sample size, and lack of prespecified diagnostic criteria for DM.

Differences among individual statins

Statin-associated NOD is considered a class effect by the FDA. Most data indicate that statin dose and potency play a role with NOD, whereas other data indicate certain agents may be less diabetogenic and demonstrate no dose dependency. One analysis noted an increased risk of NOD with rosuvastatin (hazard ratio [HR]=1.41; 95% CI, 1.31-1.52), atorvastatin (HR=1.23; 95% CI, 1.19-1.27), and simvastatin (HR=1.15; 95% CI, 1.05-1.25), but only minimal association with fluvastatin (HR=1.04; 95% CI, 0.91-1.18). Similarly, another meta-analysis noted the following odd ratios of statin associated NOD: rosuvastatin: (1.17; 95% CI, 1.02-1.35), simvastatin (1.13; 95% CI. 0.99-1.29), atorvastatin (1.13; 95% CI, 0.94-1.34), pravastatin (1.04; 95% CI, 0.93-1.16), lovastatin (0.98; 95% CI, 0.69-1.38), and pitavastatin (0.74; 95% CI, 0.31-1.77), with atorvastatin 80 mg having the highest associated risk (1.34; 95% CI, 1.14-1.57). Another study analyzed rates of NOD among Asian patients with a recent acute myocardial infarction and no DM at baseline, who were subsequently prescribed moderate-intensity statin therapy. After a follow-up period of up to 3 years, significantly more patients receiving rosuvastatin (10.4%) and atorvastatin (8.4%) had experienced NOD compared to pitavastatin (3%). Finally, the efficacy and safety of pravastatin and pitavastatin were compared in a RCT involving subjects with HIV. These specific agents were evaluated due to the challenge of treating dyslipidemia in the HIV population because of drug interactions. Neither pravastatin or pitavastatin are dependent upon the cytochrome P450 system for primary metabolism. The trial demonstrated that both treatments had neutral effects on glycemic indices in a population that is at greater risk for glycemic abnormalities and NOD.

Although data are accumulating regarding the association of statins with NOD, findings remain inconclusive. Nonetheless, statements from the FDA and EMA both indicate the risk-benefit ratio highly favors the utilization of statin therapy in at-risk patients. Further, the National Lipid Association recommends no changes to clinical practice, except to monitor glycemic indices before and after statin initiation. Finally, the Diabetes Prevention Program demonstrated the importance of modest weight loss and physical activity on glucose metabolism, as those with prediabetes were nearly 60% less likely to develop T2DM with a structured lifestyle program. These findings further support the importance of diet and exercise as the foundation for ASCVD risk reduction and the likelihood of limiting NOD when utilizing statin therapy.

EFFECT OF STATIN THERAPY ON BODY WEIGHT

Genetic variants in population studies have suggested that certain HMGCR SNPs are associated with an increase in body weight and risk of T2DM. Since statins pharmacologically inhibit HMGCR, they, too, may have similar metabolic effects. Swerdlow et al investigated this relationship both from observational data (genetic analysis) and among statin users from RCTs. The investigators found that the HMGCR...
SNPs and statin treatment were each associated with higher body weight and risk of T2DM. A second study utilized a different approach and evaluated the impact of atorvastatin and pitavastatin on non-HDL-C and the influence of body size. Similar reductions (P<.056) in non-HDL-C were noted for atorvastatin (40.3%) and pitavastatin (39%), but atorvastatin was most efficient among those with lower weight (correlation coefficient r=0.32, P=.006), body mass index (r=0.279, P=.022), and waist circumference (r=0.33, P=.034), whereas pitavastatin demonstrated a consistent reduction in non-HDL-C regardless of weight (r=0.04, P=.762), waist circumference (r=0.04, P=.822), and body mass index (r=0.05, P=.736). Collectively, these data suggest further analyses are needed to better elucidate the relationship between individual statins and body weight, and response to therapy.

**STATIN-ASSOCIATED MUSCLE SYMPTOMS**

Patient-reported musculoskeletal complaints are the major barrier to maintaining statin therapy. Approximately 10% of those prescribed statins in the United States stop therapy because of such complaints. The incidence of muscle symptoms without elevated creatine kinase in major RCTs is nearly identical between subjects receiving a statin and placebo. This strongly suggests that reported muscle symptoms are typically not statin-related. Although challenging, the AHA stresses the importance of restarting statin therapy, especially in those at high risk for ASCVD.

A thorough patient evaluation is essential to identify true intolerance prior to reintroducing a statin. Unexplained muscle symptoms with symmetric distribution occurring shortly after initiation are more likely statin-related. In such cases, several approaches can be implemented, including utilization of a different statin and alternative dosing strategies using a statin with a long elimination half-life (i.e., atorvastatin, rosuvastatin, pitavastatin), with gradual titration from once weekly to every other day dosing. Other strategies include serum vitamin D repletion and CoQ10 supplementation. Although support for each is limited, anecdotal reports indicate a possible role in practice. Supplementation with CoQ10 may possibly reverse or prevent statin-associated muscle symptoms since statins reduce plasma levels of CoQ10, with deficiencies of CoQ10 resulting in myalgia. The choice of statin may matter since individual statins appear to have different effects on plasma CoQ10 levels. Although not designed to evaluate muscle symptoms, a 12-week RCT demonstrated that, despite comparable LDL-C reductions, pitavastatin lowered CoQ10 plasma levels significantly less than atorvastatin and rosuvastatin. These data are consistent with an earlier study, noting significant reductions in CoQ10 plasma levels with atorvastatin, but not pitavastatin, even though LDL-C reductions were similar. Finally, regardless of the approach or statin utilized, direct conversations and incorporating shared decision-making when rechallenging patients are essential.

**SUMMARY**

Statin therapy continues to be the pharmacologic foundation for LDL-C reduction and ASCVD prevention. However, challenges remain with accurately identifying and stratifying ASCVD risk, especially in primary prevention populations. Clinicians must be aware of and incorporate risk-enhancing factors into practice for each individual patient to further guide treatment. Statin selection is also critical. For most patients, moderate- to high-intensity statin therapy is recommended. Further, understanding differences among individual statins is essential for proper selection. Utilizing a statin with minimal drug interactions and properties that do not aggravate risk-enhancing factors, or more importantly, effectively addressing such factors on an individual patient basis, will likely result in improved safety and patient tolerability. Monitoring adherence to lifestyle and medication use as well as LDL-C response is crucial. Most importantly, clinicians must engage the patient when discussing these factors to appropriately risk stratify and individualize statin therapy for optimal therapeutic responses.

**REFERENCES**


39. Moriarty PS, C; Backes, JM; Ruisinger, JF; Wick JA; Pitavastatin lowers plasma levels of CoQ10 less than equivalent doses of rosuvastatin or atorvastatin. Presented at: Preventative Cardiology Nurses Association 21st Annual Symposium, Orlando, FL, 2016.