Case Studies in Hyperlipidemia

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INTRODUCTION

I had a conversation with a cardiologist 15 years ago at the American College of Cardiology annual meeting during which he asked a simple question regarding patients at intermediate risk for atherosclerotic cardiovascular disease (ASCVD) – "Why wait until they see me in the cath lab after a heart attack to treat their lipids?" The point that resonated with me was to target patients at intermediate risk before they have a life-changing event or even develop angina. This simple question changed my approach to managing patients with dyslipidemia, particularly those at intermediate risk for ASCVD who make up a large subgroup of the US population.[1] In fact, because we have 2 more decades of favorable evidence from statin outcome trials including safety data, my resolve to assess and treat patients at intermediate risk for ASCVD is stronger today.[2,3] Moreover, we have learned to better risk-stratify patients with various assessment tools and incorporation of epidemiologic data supporting use of risk-enhancing factors to identify those at higher CV risk because of comorbid conditions.[3]

In this article, I provide suggestions for identifying patients classified as "intermediate risk" for preventive care. According to the American College of Cardiology (ACC)/American Heart Association (AHA), these patients have a 10-year ASCVD risk score of ≥7.5% to <20%, but because of the presence of risk-enhancing factors, have a higher overall ASCVD risk.[3] Such factors are intended to guide the clinician and influence therapy initiation and degree of lowering low-density lipoprotein cholesterol (LDL-C). Further, I provide recommendations to help navigate common clinical dilemmas when proper statin selection is imperative to avoid major drug interactions (DIs), prevent recurrence of adverse effects (AEs), and not aggravate coexisting conditions. Finally, I provide some thoughts about shared decision-making because it is essential to limit patient apprehension and achieve the individual's maximum tolerated statin and dosage.[2,3] These lessons are applicable in clinical practice as primary prevention.

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CASE SCENARIO 1

ML is a 63-year-old Hispanic female, BP 142/86 mm Hg, on amlodipine 5 mg/d, mixed dyslipidemia with an LDL-C of 110 mg/dL, high-density lipoprotein cholesterol (HDL-C) of 49 mg/dL, and triglycerides of 185 mg/dL, while taking pravastatin, 20 mg/d. She reports that she "didn't feel good" on atorvastatin, 40 mg/d, and is hesitant to try a 3rd statin. She also states, "they can cause diabetes," and is concerned the statin is putting her at a higher risk of diabetes because of her family history.

Other labs: *fasting blood glucose (FBG) 101 mg/dL, A1C 5.9%, serum creatinine (SCr) 1 mg/dL; urinary analysis and hepatic transaminases are within normal limits.*

Body mass index (BMI) *31 kg/m², waist circumference: 91.5 cm (36 inches), (-) tobacco, (-) EtOH, walks 3x/week.*

Her ACC/AHA *10-year ASCVD risk score is 7.8%.*

Family history: *both parents developed type 2 diabetes mellitus (T2DM) and ASCVD in their early 60s.*

According to the 2018 ACC/AHA Guideline on the Management of Blood Cholesterol, ML is considered "intermediate risk" because her 10-year ASCVD risk score is ≥7.5%.[3] This likely is underestimated because of factors not accounted for by the ASCVD risk calculator, including her family history of ASCVD and presence of metabolic syndrome (MetS), both of which are risk-enhancing factors.[3] Her risk score and the presence of risk enhancers indicate the need for moderate-intensity statin therapy to reduce LDL-C by 30% to 49%.

RISK-ENHANCING FACTORS FOR FURTHER RISK STRATIFICATION

To improve risk-stratification and guide initiation and

intensity of statin therapy, the 2018 ACC/AHA Cholesterol Guideline introduced risk-enhancing factors (**TABLE**).[3] The risk-enhancing factors have been identified primarily from epidemiologic data. When present, risk-enhancing factors indicate a greater overall ASCVD risk and are often proportional to the degree and duration of the specific condition. For example, the associated relative risk (RR) of ASCVD for diabetes mellitus (DM) with MetS is 2.35,[4,5] chronic kidney disease (CKD) ranges from approximately 1.4 to 3.3 depending on severity,[6,7] while systemic lupus erythematosus carries a RR of 6.4 for major cardiometabolic disease.[8] In ML's case, MetS increases her RR of ASCVD by 1.78, compared with no MetS.[4] Similarly, her family history of ASCVD, especially her mother experiencing a premature CV event (age <65), further increases ML's risk by approximately 2-fold. Therefore, her 10-year risk of a CV event is much higher than suggested by the 10-year ASCVD risk score alone.

STATIN-ASSOCIATED DIABETES MELLITUS

One component of MetS in ML is her impaired glycemic indices indicating prediabetes.[9] Her family history also is significant because both parents developed T2DM in their 60s. Understandably, ML expresses concern about statin-associated DM and does not want to further worsen her glucose parameters. Is her concern justified?

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) each released statements in 2012 about the association between statin therapy and elevated A1C and FBG,[10] and increased risk of new-onset diabetes (NOD) among those predisposed to DM.[11]

Numerous studies have solidified these statements, but with mixed results. Findings from meta-analyses of randomized-controlled trials (RCTs) have demonstrated significant but modest increases in glucose parameters.[12,13] An analysis evaluating data from 13 major RCTs noted a 9% increase in incident DM with statin therapy.[12] Conversely, a meta-analysis of observational studies reported a more robust association with statins (RR, 1.44; 95% confidence interval [CI] 1.31 to 1.58).[14] Differences among individual agents also have been evaluated, and most data indicate that statin potency and dosage play a role.[15] Specific statins appear less diabetogenic with no dose dependency.[16] Atorvastatin, rosuvastatin, and simvastatin have the strongest associations compared with minimal or no association with fluvastatin, lovastatin, pitavastatin, and pravastatin.[15] These findings are consistent with a study analyzing rates of NOD among Asian patients recently hospitalized for acute myocardial infarction and no DM at baseline.[17] During the approximately 3-year follow up, patients receiving rosuvastatin (10.4%) and atorvastatin (8.4%) reported significantly more instances of NOD compared with pitavastatin (3%).

Given the inconclusive data, the FDA and EMA indicate the risk/benefit ratio favors the use of statin therapy among patients at risk for DM.[10,11] Nonetheless, monitoring glycemic indices at baseline and during statin therapy is recommended.[13]

CASE SCENARIO 1 (CONTINUED)

Overall, ML's evaluation suggests a 10-year ASCVD risk above the 7.8% calculated by the ACC/AHA risk estimator and, therefore, the need to intensify therapy. The clinical challenge is to balance the need for more intensive therapy without reintroducing previously experienced statin AEs or aggravating the patient's already impaired glucose. If unsuccessful, medication nonadherence commonly manifests, resulting in elevated LDL-C and poor clinical outcomes.[18] ML's current lipid therapy is pravastatin, 20 mg/d, and although she reports no AEs, the agent is classified as a low-intensity statin with LDL-C reduction of <30%.[3] Because of her ASCVD risk, consider a safe, moderate-intensity statin that provides a 30% to 49% reduction in LDL-C and does not predispose her to a higher risk of NOD should be considered. Reasonable options include titrating to pravastatin 80 mg/d, or switching to pitavastatin, 2 to 4 mg/d, or rosuvastatin, 5 to 10 mg/d. To maintain adherence, shared decision-making and counseling regarding the risk/benefit ratio of statin therapy, including that the new statin is unlikely to worsen her glycemia, is essential.

CASE SCENARIO 2

RJ is a 56-year-old white male with human immunodeficiency virus (HIV) on antiretroviral therapy (ART).

BP 148/88 mm Hg, repeat 146/86 mm Hg (hypertension not treated).

Labs/procedures: *FBG 99 mg/dL, A1C 5.8%, SCr 1.2; hepatic transaminases, urinary analysis, prostate-specific antigen, and colonoscopy – all WNL.*

Lipid panel: *total cholesterol (TC) 192 mg/dL, HDL-C 46 mg/dL, triglycerides 180 mg/dL, LDL-C 110 mg/dL, non-HDL-C 146 mg/dL (all values similar to last 2 lipid profiles).*

BMI *29 kg/m^2, waist circumference 101.6 cm (40 inches), (-) tobacco (quit last year – 60-pack-year history), (+) EtOH 2 drinks/week, no formal exercise.*

Patient reports taking simvastatin in his 40s but discontinued because of fatigue and myalgias.

ACC/AHA *10-year ASCVD risk score 7.7%.*

Family history *is complicated by tobacco and alcohol abuse. He is aware of DM and ASCVD in the family, although details are limited.*

RJ has a mixed dyslipidemic pattern and is at intermediate risk of a primary event. His ASCVD risk score of 7.7% likely underrepresents his true risk because of the presence of numerous

TABLE. **General risk-enhancing factors for additional risk stratification[2]**

- **Family history of premature ASCVD** (males, age <55; females, age <65)
- **Primary hypercholesterolemia** (LDL-C 160-189 mg/dL; non-HDL 190-219 mg/dL)
  - **Metabolic syndrome** (increased waist circumference, elevated triglycerides (≥150 mg/dL), elevated blood pressure, elevated fasting blood glucose, and low HDL-C (<40 mg/dL in men; <50 mg/dL in women) are factors; >3 makes the diagnosis
- **Chronic kidney disease** (eGFR 15 to 59 mL/min/1.73 m_2, with or without albuminuria; not treated with dialysis or kidney transplant)
- **Chronic inflammatory conditions** such as psoriasis, RA, HIV/AIDs
- **History of premature menopause (age <40) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia**
- **High-risk race/ethnicities** (eg, South Asian ancestry)
- **Lipid/biomarkers:** associated with increased ASCVD risk
  - **Persistently* elevated, primary hypertriglyceridemia** (≥175 mg/dL)
  - **If measured:**
    - **Elevated high-sensitivity C-reactive protein** (≥2 mg/L)
    - **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)
    - **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 >160 mg/dL and constitutes a risk-enhancing factor
    - **Ankle-brachial index** <0.9

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

[a]Or on drug treatment for noted condition is also an indication

risk-enhancing factors including HIV, MetS, persistently elevated triglycerides, and possible family history of premature ASCVD.[3] According to the 2018 ACC/AHA Cholesterol Guideline, initiation of a moderate-intensity statin for an LDL-C reduction of 30% to 49% is favored because of his ASCVD risk score and multiple risk-enhancing factors.[3] For example, his HIV status elevates his ASCVD risk by nearly 3-fold compared to non-infected individuals, secondary to chronic inflammation and comorbid (mixed) dyslipidemia.[19] In addition, persistently elevated triglycerides are associated with a 1.37 RR increase in ASCVD.[20] As noted in case 1, a family history of premature ASCVD and MetS also increases RR of ASCVD by approximately 2.0 and 1.78, respectively.

DRUG INTERACTIONS

Statin-related AEs generally are not idiosyncratic in nature, but are caused by increased serum concentrations often resulting from a drug interaction.[21] Statin metabolism is a complex, multi-step process. The cytochrome P450 (CYP450) system plays a major role in metabolism as it does for several other drugs.[22] Approximately 75% of all medications are metabolized via CYP450, with 50% of such agents having affinity for the common CYP3A4 isoenzyme.[23] Current FDA labeling indicates lovastatin, simvastatin, and, to a lesser degree, atorvastatin most subject to DIs because of their high affinity for the CYP3A4 isoenzyme.[24-26] The remaining statins have less risk of major DIs.[22] Clinically relevant CYP3A4 inhibitors include azole antifungals, amiodarone, clarithromycin, erythromycin, HIV protease inhibitors (eg, boceprevir, telaprevir), diltiazem, verapamil, and grapefruit juice.[21,22,27]

Statin metabolism involves more than the CYP450 system. Other common drug transporters that may be involved include breast cancer-resistant protein (BCRP), P-glycoprotein (P-gp), organic anion-transporting polypeptides (OATPs), and multi-drug-resistant protein.[21,22] Inhibition of drug transporters, such as OATP1B1 and P-gp can also increase statin exposure. All statins are substrates for OATP transporters, especially OATP1B1, and common inhibitors include cyclosporine, erythromycin, and gemfibrozil. Importantly, cyclosporine inhibits multiple steps (eg, BCRP, OATP1B1, CYP3A4) in statin metabolism and can markedly elevate statin serum concentrations.[21,22] Further, cyclosporine has been implicated in many cases of rhabdomyolysis when co-administered with a statin.[28] Of all agents, cyclosporine may carry the most risk for major statin DIs and related AEs.[22]

In the case of RJ, his HIV status should alert the clinician to the importance of individualizing therapy due to the potential for major DIs and statin-related AEs.[22] The HIV population is especially prone to DIs because of complex medi-

cation regimens including the use of protease inhibitors. The FDA published a Drug Safety Communication in 2012 advising that the concomitant use of statins and protease inhibitors, which are commonly used for treating patients with HIV and hepatitis C virus, increases the risk of myopathy and rhabdomyolysis.[27] These cautions are included in current statin labeling.[24-27,29-32]

Similar to previously discussed CYP3A4 interactions, certain statins are contraindicated (lovastatin, simvastatin) with concomitant HIV protease inhibitors, while others have dose limitations and/or should be avoided depending on the interacting protease inhibitor (rosuvastatin, atorvastatin).[27] Information for fluvastatin is not available. Alternatively, pitavastatin and pravastatin have no limitations, precautions, or contraindications with HIV protease inhibitors.[22,27]

The HIV population is understudied with limited statin options, but are at significant risk for ASCVD because of risk-enhancing factors (eg, chronic inflammation, MetS).[19] The National Institute of Allergy and Infectious Disease is conducting a landmark outcome trial (REPRIEVE) involving 7770 patients that compares the effects of pitavastatin with placebo on composite CV events; results are expected in 2023.[33]

Because of the complexities of statin metabolism, there are 2 key areas to help the clinician recognize common DI pitfalls: 1) medications that are commonly used and have the most potential to inhibit statin metabolism, and 2) differences among individual statins regarding metabolic pathways. Using this practical approach should alert the clinician to high-risk medications, in hopes of preventing the negative outcomes associated with major statin DIs. To help guide prescribing and limit the risk of muscle injury, the FDA published 2 additional Drug Safety Communications involving restrictions on simvastatin and lovastatin.[10,34] For a more comprehensive discussion on clinically important statin DIs, see Kellick et al.[22]

CASE SCENARIO 2 (CONTINUED)

The risk of ASCVD for RJ is likely greater than the 7.7% determined from the ACC/AHA 10-year risk estimator. In addition to his noted risk-enhancing factors, MJ has an extensive smoking history, probable hypertension, and prediabetes. A structured lifestyle program could potentially improve the latter 2 risk factors.[2] The Diabetes Prevention Program demonstrated the benefits of exercise and modest weight loss on glucose metabolism. Those with prediabetes who adopted a structured lifestyle program have been shown to be nearly 60% less likely to develop T2DM.[35] Such findings emphasize the importance of diet and exercise for cardiometabolic conditions and the likelihood of limiting NOD with statin therapy.[2,3]

Given RJ's ASCVD risk, a moderate-intensity statin or maximally tolerated statin would be primary prevention to reduce the risk of a major CV event.[3] Being aware of potential DIs with his ART and previous intolerance is important. Appropriate choices from the FDA to safely reduce LDL-C by 30% to 49% include pitavastatin, 1 to 4 mg/d, or pravastatin, 40 to 80 mg/d, or limiting rosuvastatin to 5 to 10 mg/d.[27] It is possible that his previously reported statin AE might have been secondary to coadministration of simvastatin and ART, and markedly elevated simvastatin levels. Because RJ has a history of statin intolerance, consider starting with a lower dosage and gradually increasing. Other options to manage statin intolerance include initiating a long half-life agent (eg, atorvastatin, rosuvastatin) with an alternative dosing schedule such as twice weekly with gradual increase as tolerated. Adding ezetimibe would provide additional LDL-C reduction and generally does not worsen statin-related AEs.[36]

CASE SCENARIO 3

FF is a 59-year-old African American female with a family history of premature ASCVD (her father had a myocardial infarction at age 48). She is taking hydrochlorothiazide, 25 mg/d, for hypertension (average BP at home 138/68 mm Hg). Since her early 40s, she also has taken methotrexate, 12.5 mg once weekly, and glucosamine/chondroitin daily for rheumatoid arthritis (RA).
She follows a low-sodium diet; exercise involves daily stretching and walking for 20 minutes most days.
***BMI** 28 kg/m^2, (-) EtOH, (-) tobacco.*
***Labs:** hepatic transaminases, SCr, thyroid stimulating hormone and A1C - all WNL, high-sensitivity C-reactive protein (hsCRP) 3.8 mg/L, lipids: TC 194 mg/dL, HDL-C 53 mg/dL, triglycerides 135 mg/dL, LDL-C 114 mg/dL, non-HDL-C 141 mg/dL, lipoprotein (a) [Lp(a)] 56 mg/dL.*
***ACC/AHA** 10-year ASCVD risk score 8.0%.*

Once again, we have a patient at intermediate risk of a CV event with ASCVD risk greater than indicated by her ASCVD risk score of 8.0%.[3] Her notable risk-enhancing factors include a family history of premature ASCVD, chronic inflammation from RA, elevated hsCRP, and elevated Lp(a). The presence of RA elevates the RR of major cardiometabolic disease by 1.7.[8] Lp(a) is not routinely drawn and RR is variable, but measuring can be considered in those with a family history of premature ASCVD.[3] Further, her overall lipid profile is fairly unremarkable, possibly providing a false sense of limited ASCVD risk. Nonetheless, this is a patient that would benefit from statin therapy and LDL-C reduction of 30% to 49%.[3]

A common clinical challenge in patients such as FF is a hesitation to start a statin because her "cholesterol is fine." In such cases, measuring coronary artery calcium (CAC) or carotid intima-

Pearls and Pitfalls: Key Take-Home Messages

- Don't wait to start statin therapy until after a patient at intermediate risk has had a CV event.
- Most females age >55 or age males >45 years with ≥2 CV risk factors are at intermediate risk.
- The 10-year ACC/AHA risk estimator alone could underestimate an individual patient's CV risk.
- Including risk-enhancing factors provides a more accurate assessment of overall CV risk.
- The case scenarios demonstrate patients at "intermediate risk" with a wide range of 10-year ASCVD risk scores ≥7.5% to <20%, and how risk factors and enhancers are intended to guide therapy and intensity.
- The presence of 1 risk-enhancing factor can elevate the RR of ASCVD by approximately 1.25 to >6-fold.
- Patients at intermediate risk with unremarkable lipid profiles, but risk-enhancing factors, commonly "fall through the cracks" for ASCVD prevention.
- Individually risk-stratifying patients and individualizing statin selection are imperative for safe and effective LDL-C reduction.
- Some patient populations (eg, HIV) have elevated ASCVD risk, are prone to major DIs because of complex medication regimens, and have limited statin options.
- Be cognizant of statins metabolized by CYP3A4 (lovastatin, simvastatin, atorvastatin) and the potential for major DIs and significant statin-related AEs. Similarly, note other commonly prescribed agents (eg, cyclosporine, gemfibrozil, erythromycin) that are implicated in major statin DIs.
- Measure CAC or CIMT to further refine assessment if the risk decision is uncertain or issues surrounding statin therapy are present.
- We now have 3-plus decades of favorable statin outcome trials, including safety data. This is useful information when discussing the risk/benefit of statin therapy with patients.
- Engaging the patient in shared decision-making is especially helpful in patients who "feel fine" but are at increased CV risk or have experienced a statin-related AE and resist statin therapy.

media thickness (CIMT) to determine degree of atherosclerosis can help inform the decision.[3,37] The presence of substantial atherosclerotic burden with either measure favors initiation of statin therapy and the visualization of disease often resonates with patients.[37] Additionally, the inherent musculoskeletal complaints from her RA can be misinterpreted as statin associated myalgia. Patient counseling noting the presence of baseline myalgias and arthralgias can be helpful if the patient subsequently reports muscle-related symptoms thought to be from statin therapy.[18]

A frank clinician-patient risk discussion and shared decision-making when initiating statin therapy cannot be overemphasized. As part of this process, it is important to invite the patient to share their understanding of the disease and concerns they may have. FF is an example of a patient with an intermediate risk and significant risk-enhancing factors who would likely benefit from this type of discussion. Since she believes her "cholesterol is fine," informing her of the factors beyond cholesterol that elevate ASCVD risk, including her father's myocardial infarction at age 48 years, the chronic inflammation from her RA, and elevated Lp(a), would provide key insight and allow for a more informed decision. Finally, it is important to stress that the higher the ASCVD risk, the greater the benefit from statin therapy.[3] An informed patient who feels she has been part of the decision-making process is more likely to be adherent to therapy, resulting in improved clinical outcomes.[3] ●

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