Individualizing Treatment with Statin Therapy

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INTRODUCTION

Statin therapy remains the pharmacological foundation for the management of elevated low-density lipoprotein cholesterol (LDL-C). This is due to an established record of safety with lowering LDL-C, and supported by a host of outcome trials indicating a significant reduction in major cardiovascular (CV) events. Yet, many challenges and questions still exist in clinical practice. To aid in the optimal management of elevated LDL-C levels, medical associations have developed guidelines or recommendations with a focus on patient-centric care (TABLE 1).1-4

A key challenge for any target condition is individual risk assessment of patients for primary prevention. Performing risk scoring to estimate 10-year atherosclerotic cardiovascular disease (ASCVD) risk helps stratify patients in determining appropriate lipid targets and statin intensity. Most notable is the American College of Cardiology (ACC) ASCVD risk estimator,1 which recommends moderate- to high-intensity statin (TABLE 2) therapy for those with 10-year ASCVD risk of ≥7.5%. Such recommendations align with the general principles that the intensity of risk-reduction therapy should be adjusted to the patient’s absolute ASCVD risk and that the benefit of risk reduction is proportional to the extent of LDL-C reduction.1,2 Moreover, limited data exist on managing certain complex populations. For example, individuals with human immunodeficiency syndrome (HIV) have inherently high CV risk, yet remain understudied.

Three decades of statin data and guideline revisions have shown how critically important it is to take a patient-centric approach by individualizing treatment so as to improve adherence and, ultimately, patient care.

DIFFERENTIATING AMONG STATINS

Effectiveness in LDL-C lowering

It is imperative to assess individual patient characteristics and needs when prescribing statins. Selecting among the statins, as well as the statin dose, requires the clinician to find the “best fit” to limit adverse effects (AEs), improve long-term adherence, and ultimately reduce ASCVD events. A key differentiation among the statins is their effectiveness in lowering LDL-C, with dose intensity based on desired percent LDL-C reduction (TABLE 2) and corresponding to the overall 10-year ASCVD risk.1,2 In general, moderate- to high-intensity statins are recommended for patients with a 10-year ASCVD risk score ≥7.5% or who have previously experienced a CV event. Moderate-intensity statins can also be considered for patients with a 10-year ASCVD risk score of 5% to <7.5%. Moderate-intensity statins result in a 30% to <50% reduction in LDL-C, whereas high-intensity agents reduce LDL-C by ≥50%. The National Lipid Association (NLA) also stresses the importance of non-high-density lipoprotein cholesterol

LEARNING OBJECTIVES

After participating, the clinician will be able to:

• Clarify the role of statins in the treatment of elevated low-density lipoprotein cholesterol (LDL-C) according to current guidelines and other recommendations

• Individualize statin therapy based on patient needs and characteristics

DISCLOSURES

Dr. Bays discloses that he is on the advisory boards for Aplylam Pharmaceuticals, Inc.; Akcea Therapeutics; Amgen Inc.; AstraZeneca; Eisai Co., Ltd.; Eli Lilly and Company; Esperion; Ionis Pharmaceuticals (ISIS); Janssen Pharmaceuticals, Inc.; Johnson & Johnson; Kowa Pharmaceuticals America, Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; ProSciento; Regeneron Pharmaceuticals, Inc.; and sanofi-aventis U.S. LLC. He is on the speakers’ bureaus for Amarin Corporation; Amgen Inc.; Eisai Co., Ltd.; Kowa Pharmaceuticals America, Inc.; Orexigen Therapeutics, Inc.; Regeneron Pharmaceuticals, Inc.; and sanofi-aventis U.S. LLC.

Dr. Cobble discloses that he is on the advisory board for Kowa Pharmaceuticals America, Inc. and on the speakers’ bureaus for Amarin Corporation; Amgen Inc.; AstraZeneca; Kowa Pharmaceuticals America, Inc.; Regeneron Pharmaceuticals, Inc.; and sanofi-aventis U.S. LLC.

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TABLE 1 Comparative highlights of major lipid guidelines and recommendations

<table>
<thead>
<tr>
<th>ACC/AHA1 2013</th>
<th>NLA2 2014</th>
<th>USPSTF4 2016</th>
<th>AACE/ACE3 2017</th>
</tr>
</thead>
</table>
| **Primary targets: non-HDL-C and LDL-C**
| Recommended moderate- or high-intensity statin | | | |
| Treatment goals: (mg/dL) | | | |
| Risk non-HDL-C<sup>c</sup> LDL-C<sup>d</sup> | | | |
| Low | <130 | <100 | |
| Moderate | <130 | <100 | |
| High | <130 | <100 | |
| Very high | <100 | <70 | |
| Criteria for ASCVD risk assessment | | | |
| Risk | Criteria | | |
| Low | 0-1 ASCVD RFs<sup>b</sup> | | |
| Moderate | 2 ASCVD RFs<sup>b</sup> | | |
| High | ≥3 ASCVD RFs<sup>b</sup> or DM + (0-1 ASCVD RFs<sup>b</sup> or stage 3B/4 CKD or LDL-C ≥190 mg/dL) | | |
| Very high | ASCVD DM + (≥2 ASCVD RFs<sup>b</sup> or end organ damage) | | |

Primary prevention
- Age 40-75 y with no history of CVD, ≥1 CVD risk factor, and estimated 10-y ASCVD risk 7.5%-10%: selectively offer low-to moderate-dose statin
- Age 40-75 y with no history of CVD, ≥1 CVD risk factor, and estimated 10-y ASCVD risk ≥10%: initiate low- to moderate-dose statin
- Age ≥75 y with no history of CVD: no recommendation due to insufficient evidence
- LDL-C >190 mg/dL: may require statin use
- Familial hypercholesterolemia: may require statin use

Primary targets: LDL-C and non-HDL-C
- Endorsed 10-yr ASCVD risk prediction using various assessment calculators
- Statins are recommended as the primary drug therapy for achieving LDL-C goals
- Introduced ‘extreme risk’ category and aggressive lipid targets – patients with:
  - Progressive ASCVD despite LDL-C <70<sup>e</sup>
  - ASCVD + DM, CKD (Stages 3/4) or HeFH
  - History of premature ASCVD
  - Lipid targets:
    - LDL-C <55<sup>e</sup>
    - Non-HDL-C <80<sup>c</sup>

**Statin safety**

Treatment safety and patient tolerability are key considerations in developing a treatment plan. Differences among the statins provides an opportunity to individualize therapy and give patients the best chance of staying on lifelong treatment to prevent ASCVD. When safety or tolerability issues preclude continued use of one statin, switching to another statin with attributes that are aligned with the individual patient should be considered before leaving the statin class for other lipid-modifying agents. For example, switching to a statin with low potential for DIs in a patient with polypharmacy limits safety concerns and the likelihood of concentration-dependent AEs.

**Safety and tolerability**

Although numerous factors can affect statin safety and tolerability, statins have an overall favorable safety profile. Severe

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<sup>1</sup>*mg/dL

<sup>2</sup>Major risk factors = age (male ≥45 y, female ≥55 y), family history of early ASCVD (<55 y of age in a male first-degree relative or <65 y in a female first-degree relative), (+) cigarette smoking, high blood pressure (≥140/90 mm Hg, or on blood pressure medication), and low HDL-C (male <40 mg/dL, female <50 mg/dL).

<sup>3</sup>non-HDL-C = total cholesterol – HDL-C

Abbreviations: AACE, American Association of Clinical Endocrinologists; ACC, American College of Cardiology; ACE, American College of Endocrinology; ACS, acute coronary syndrome; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetSyn, metabolic syndrome; NLA, National Lipid Association; NEs, risk equivalents; RFs, risk factors; y, year.
Statin-intensity categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Statin Intensity</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-intensity — dosed daily</td>
<td>LDL-C ≥50%</td>
<td>Atorvastatin 40-80 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rosuvastatin 20-40 mg</td>
</tr>
<tr>
<td>Moderate-intensity — dosed daily</td>
<td>LDL-C 30 to &lt;50%</td>
<td>Atorvastatin 10-20 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluvastatin 40 mg bid</td>
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<tr>
<td></td>
<td></td>
<td>Fluvastatin XL 80 mg</td>
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<tr>
<td></td>
<td></td>
<td>Lovastatin 40 mg</td>
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<tr>
<td></td>
<td></td>
<td>Pitavastatin 2-4 mg</td>
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<td></td>
<td></td>
<td>Pravastatin 40-80 mg</td>
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<tr>
<td></td>
<td></td>
<td>Rosuvastatin 5-10 mg</td>
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<tr>
<td></td>
<td></td>
<td>Simvastatin 20-40 mg</td>
</tr>
<tr>
<td>Low-intensity — dosed daily</td>
<td>LDL-C &lt;30%</td>
<td>Simvastatin 10 mg</td>
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<td>Pravastatin 10-20 mg</td>
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<td>Lovastatin 20 mg</td>
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<td>Fluvastatin 20-40 mg</td>
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<tr>
<td></td>
<td></td>
<td>Pitavastatin 1 mg</td>
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</tbody>
</table>

Abbreviations: bid, twice daily; LDL-C, low-density lipoprotein-cholesterol.


AEs resulting in hospitalizations (ie, rhabdomyolysis) are very rare with an estimated annual incidence of 0.44 per 10,000 person-years with statin monotherapy. Safety and tolerability are important considerations for statin therapy since, whether real or perceived, AEs are the primary reason for statin discontinuation.

This is important since statin discontinuation is associated with higher rates of ASCVD. Statin safety and potential AEs are common topics in the medical literature and mainstream media. As such, the US Food and Drug Administration (FDA) and the NLA have provided updates including potential risks of statin use.

When statin therapy results in a major AE, an underlying DI is frequently implicated. Drug interactions are well established with the individual statins.

Most worrisome are concomitant medications that may increase statin levels by several-fold, resulting in concentration-dependent AEs (FIGURE) (see Drug Interactions on page S46). Those with advanced age are perhaps most at risk for DIs due to polypharmacy and comorbidities, and AEs may be most debilitating in patients age ≥65 years.

Statin intolerance

One limitation of statin therapy is statin intolerance. Although there is no universally agreed upon definition, the NLA defines statin intolerance as “adverse symptoms, signs, or laboratory abnormalities attributed by the patient (or provider) to the statin and in most cases perceived by the patient to interfere unacceptably with activities of daily living, leading to a decision to stop or reduce statin therapy.” Switching to another statin is also an option.

Statin intolerance due to musculoskeletal complaints typically involves myalgias or myopathy, with the latter being associated with elevated creatine kinase (CK) levels. In most instances, patients report myalgias, with normal CK values.

The incidence of statin-associated muscle symptoms (SAMS) is widely variable and not well-defined, but is estimated to affect approximately 15% of statin users.

Statin intolerance can frequently be attributed to patient perception or other underlying medical conditions, comorbidities, and concomitant therapies. Nonetheless, there are certain patients that have a true sensitivity and are unable to tolerate any level of statin therapy. However, before a patient is considered statin intolerant, the exclusion of other potential causes of muscle-related symptoms (eg, hyperuricemia, hypothyroidism, vitamin B12 and/or D deficiency, inflammatory diseases, and non-statin-related musculoskeletal disorders) is warranted.

Muscle-associated symptoms or injury

The primary barrier to statin therapy is patient-reported musculoskeletal complaints. The clinical presentation of SAMS is highly subjective, as CK levels are typically normal, and involves a spectrum of symptoms, which overlap with common musculoskeletal conditions. Moreover, SAMS negatively impacts outcomes as discontinuation or down-titration of statin therapy is associated with higher rates of ASCVD. Various tools and approaches have been developed to determine if symptoms are statin-related and to assist with management.

One such tool is the Statin Myalgia Clinical Index (SMCI), which has recently been revised. Key features of the SMCI suggesting statin etiology include symmetric distribution of unexplained muscle symptoms, symptom onset shortly after initiation, improvement within 2 weeks after dechallenge, and symptom recurrence within 4 weeks of rechallenge. If the symptoms are determined to be statin-related, numerous approaches can be utilized including trying a different statin, implementing an alternate dosing strategy (such as once-weekly dosing) with a statin that has a long half-life (ie, atorv-
A key step to individualizing statin therapy is awareness of potential DIs. Multiple steps are involved in statin metabolism (FIGURE). In addition to the well-described cytochrome P450 (CYP) enzyme system, numerous drug transporters are involved in statin metabolism, including multidrug-resistant-associated proteins, breast cancer-resistant proteins, P-glycoproteins, OATPs, and organic cationic transporters (OCTs). The potential for hepatotoxicity with lipid-altering agents has historically been a concern for clinicians and, more recently, patients.\(^\text{15}\) However, in 2012, the FDA removed the need for routine periodic monitoring of hepatic enzymes in all statin labeling.\(^\text{9}\) Instead, the FDA recommended that LFTs only need to be performed prior to initiating statin therapy, and as clinically indicated thereafter.

**FIGURE**  Steps involving statin metabolism.


circulation $\rightarrow$ Polar drug conjugates $\rightarrow$ Liver $\rightarrow$ Portal Blood Vessels $\rightarrow$ Intestine $\rightarrow$ CYP450 enzymes $\rightarrow$ Transporter $\rightarrow$ OATPs, etc. $\rightarrow$ Bile $\rightarrow$ Urine

Phase 1 drug metabolism: Oxidation, reduction, and/or hydrolysis via cytochrome P450 enzymes

Phase 2 drug metabolism: Conjugation via glucuronidation, acetylation, glutathione conjugation, sulfate conjugation, methylation

Phase 3 drug metabolism: Distribution and elimination of drugs mediated by transporters

Cytochrome P450 enzymes (CYP450) = via microsomal/endoplasmic reticulum; most common CYP450 isozyme for drug metabolism is CYP450 3A4

Organic Anion-Transporting Polypeptides (OATP) = Organic anion-transporting polypeptides, including OATP1B1, facilitate drug movement in and out of intestinal cells and into liver cells; organic cationic transporters facilitate drugs movement in and out of the intestinal cells, and from the blood into the intestine and into the liver

Multidrug-Resistant-associated Proteins (MRP) = facilitate drug movement from intestinal cells into the blood

P-glycoproteins (P-gp) = facilitate drug movement from intestinal cells into the intestinal lumen, and from the liver into the bile

Breast Cancer-Resistant Proteins (BCRP) = facilitates drug movement from intestinal cells into the intestinal lumen, and from the liver into the bile

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Statins have been implicated in cases of severe hepatotoxicity, but the incidence is exceedingly rare. A population-based study evaluated the incidence of hospitalization due to drug-induced acute liver failure among ~5.5 million patients.\(^\text{10}\) Of 32 cases identified over a 6-year period, nearly 80% implicated either acetaminophen or dietary supplements, while two involved statin therapy, along with other concomitant agents. For managing potential statin-associated hepatotoxicity, repeating LFTs to confirm persistent elevations and using sound clinical judgment are the most critical.\(^\text{17}\)

**CASE SCENARIO #1**

JS is a 63-year-old male being seen for a follow-up visit. He has been taking simvastatin 20 mg/day for the past year; LDL-C is now 106 mg/dL.

At last visit 3 months ago, he was started on verapamil for hypertension, which is now controlled. His 10-year ASCVD risk score is 16.6%, but he is otherwise healthy. Today, he is complaining of achy muscles that make it hard for him as a custodian at a local school. JS notes that he is not sure he wants to continue statin therapy and is uncertain whether he really needs it.
for their metabolism are pitavastatin and pravastatin and thus, may have a reduced potential for significant DIs.12

**CASE SCENARIO #1 (CONTINUED)**

This case presents a common scenario in which a DI may have occurred with the addition of verapamil to simvastatin, which may have contributed to the patient’s subsequent hesitancy to continue statin therapy. It also underscores the patient’s limited understanding of his ASCVD risk. Discussing his 10-year risk score can be used to improve his understanding and hopefully motivate him to agree to further treatment for his elevated LDL-C. Verapamil could be discontinued and the patient switched to another antihypertensive medication that is not metabolized via CYP3A4. If this is done, the dose of simvastatin should be increased to provide additional LDL-C reduction. Alternatively, the simvastatin could be discontinued and the patient switched to another statin that is not metabolized via CYP3A4 at a dose that would provide additional LDL-C reduction.

Another key metabolic step with statins is hepatic uptake with OATPs, especially OATP1B1.12 All statins are substrates for OATP1B1 (FIGURE). Common inhibitors of OATP1B1 include cyclosporine, erythromycin, and gemfibrozil. Cyclosporine not only inhibits OATP1B1 but other statin metabolic pathways and may increase statin concentrations several-fold. As such, cyclosporine should generally be avoided with statins. Although statin concentrations are only modestly increased (1-2-fold) with gemfibrozil, concomitant use of statins and gemfibrozil should be avoided or recommended dose limits should be followed for certain agents.12

**CASE SCENARIO #2**

MR is a 46-year-old male presenting for follow-up. His past medical history is significant for HIV, poorly controlled type 2 diabetes mellitus (DM), hypertension, atrial fibrillation, and depression. Other notable information is a family history of premature ASCVD, current tobacco use (1 pack/day), no alcohol intake, and a 10-year ASCVD risk score of 24%. MR reports no recent hospitalizations but admits that he is concerned regarding his future health, given his HIV status and family history of early ASCVD. Current labs indicate a mixed dyslipidemic pattern with an LDL-C of 110 mg/dL; C-reactive protein is moderately elevated. Medications of interest include his HIV protease inhibitors lopinavir + ritonavir, amiodipine, warfarin, but no antihyperlipidemic agents.

Certain populations are prone to DIs and potential statin-related AEs. These include patients taking multiple medications or conditions requiring complex drug regimens such as HIV infection and solid organ transplants. For those with HIV and taking protease inhibitors, the FDA has provided guidance on the use of statins to limit DIs.19 Most statins have dose limits (rosuvastatin, atorvastatin), are contraindicated (lovastatin, simvastatin), have no data available (fluvastatin), or should be avoided with certain HIV protease inhibitors (atorvastatin). Conversely, pitavastatin and pravastatin have no dose limits or additional precautions with concomitant use of HIV protease inhibitors. The HIV population is also at significant risk for ASCVD secondary to HIV, comorbid dyslipidemia, and chronic inflammation.20 Epidemiologic data indicate that those with HIV infection have a 2-fold increased rate of CV events relative to non-infected patients.20 To best answer the question of the benefit of statins in preventing ASCVD in this understudied population at high risk for ASCVD, the National Institute of Allergy and Infectious Diseases and Division of AIDS is currently conducting a landmark outcome trial comparing the effects of pitavastatin versus placebo on composite CV events (REPRIEVE).21

**CASE SCENARIO #2 (CONTINUED)**

MR is an example of a patient with significant ASCVD risk and requiring a complicated medication regimen. His 10-year ASCVD risk score of 24% may be underestimated since most risk calculators do not factor in premature family history of ASCVD and inflammatory measures,1,2 nor do they factor in HIV infection. The clinician must recognize the need for statin therapy and the need to stop smoking, but also be aware of the potential for major DIs and severe AEs. Given his ASCVD risk, implementing a safe, moderate-intensity statin for LDL-C reduction of 30% to 49% may be considered.

Clinicians must understand statin-related DIs, especially among populations requiring complex drug regimens. It is imperative to avoid critical combinations of the statins most prone to DIs (ie, lovastatin, simvastatin, atorvastatin) with specific agents having the highest potential for increasing statin concentrations (eg, azole antifungals, macrolides, cyclosporine, gemfibrozil, HIV protease inhibitors). Further, certain statins (eg, rosuvastatin, simvastatin) inhibit warfarin clearance, thus increasing the potential for bleeding during statin treatment initiation.12 Awareness of such interactions may limit statin-related AEs and potentially improve adherence and long-term outcomes.

**New onset diabetes**

Consistent with earlier observations, a small but significant association between new onset diabetes (NOD) and rosuvastatin therapy was observed in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study.22 A subsequent meta-analysis confirmed this small but significant link as statin therapy was associated with a 9% increased risk for incident DM.23 An additional analysis by Preiss et al evaluated statin dose and
determined that high-dose statin therapy was associated with a 12% greater likelihood of NOD compared to moderate dose therapy.24 In 2013, a comprehensive meta-analysis further confirmed a dose-dependent link with NOD and a gradient of risk across many different individual statins.25 Overall, most data indicate a modest increase in NOD (10%-12%) with several statin therapies, particularly among those at risk for DM.26 In terms of number needed to harm, one meta-analysis of randomized controlled trials (RCTs) (N=91,140) found that treating 255 patients with statin therapy for 4 years would yield one additional case of DM.23 Conversely, a few observational studies note higher rates and a stronger correlation, suggesting that de-prescribing statin therapy in certain populations (ie, women age >75 years) may be advisable.27,28

The FDA considers statin-associated NOD a class effect,9 but most data suggest the link is secondary to dose and each statin.29 Zaharan et al found significantly higher rates of NOD with atorvastatin (HR, 1.25; P<.0001), rosuvastatin (HR, 1.42; P<.0001) and simvastatin (HR, 1.14; P=.0005) compared to pravastatin (HR, 1.02; P=NS) and fluvastatin (HR, 1.04; P=NS).29 A meta-analysis of pitavastatin RCTs, including doses up to 8 mg daily, found no adverse effect on glucose metabolism or NOD.30

Cognition

Limited data have suggested an association between statins and cognitive impairment (CI), prompting labeling changes to all statins in 2012. The FDA indicated that post-marketing AE reports “…described individuals over the age of 50 years who experienced notable, but ill-defined memory loss or impairment that was reversible upon discontinuation of statin therapy.”29

The FDA stressed the rarity of these events and that there is no evidence to indicate progression to dementia. At worst, a weak causal effect is suggested. Conversely, other data have suggested a neutral or protective effect on cognition with statin therapy.31,32 For example, an analysis of a possible association between statins and Alzheimer’s disease among Medicare beneficiaries (N=399,979)32 showed that patients with high statin exposure had a significantly lower risk of developing Alzheimer’s disease (HR, 0.85-0.88; P<0.01) compared to those with minimal statin exposure. Overall findings involving statin therapy and cognitive effects are mixed. If statin associated CI is suspected, ruling out other causes is warranted. If symptoms persist following statin discontinuation, neuropsychological testing can be considered.

SUMMARY

Statins are endorsed as first-line therapy by numerous authorities for LDL-C reduction and prevention of ASCVD. For optimal management, statin intensity should provide the LDL-C reduction needed based on the patient’s overall ASCVD risk. Statins possess a favorable safety profile, yet musculoskeletal complaints are a major barrier, often resulting in discontinuation of statin therapy. Certain statins are prone to significantly more severe DIs based on metabolism and can result in dose-dependent AEs. Clinicians must be aware of these factors to appropriately individualize therapy for optimal patient outcomes. 

REFERENCES