"Latest Update on Statins for Diabetes".

Module 6

Optimizing Statin Therapy Dosing, Duration, and Monitoring

CONTENT

Introduction

Cardiovascular disease is the most common cause of death in the United States and worldwide. Most of this disease is preventable with improvement of lifestyle and medication to reduce circulating cholesterol. The most common medications prescribed to reduce cholesterol are statins, which inhibit the hepatic enzyme HMG-CoA reductase, the limiting enzyme in cholesterol synthesis. Unfortunately, statins are rarely prescribed correctly, resulting in excessive adverse events and very poor patient compliance. In fact, studies have demonstrated that approximately 50% of patients prescribed statins are no longer taking the medication within 1 year of obtaining a prescription.1 This omission results in less than half of all "at risk" patients achieving national guideline low-density lipoprotein (LDL) cholesterol goals, thereby resulting in excessive cardiovascular mortality.

In 2019, a description of the pitfalls of statin prescribing was published.2 Since that Commentary, new studies of statin use have shown additional advantages of maintaining a lower statin dose with the addition of ezetimibe to enhance statins' LDL cholesterol-lowering activity.3 Correct statin prescribing is not difficult but does require an understanding of statins' metabolic effects at the liver, the intestine, and muscle. The goal of this Commentary is to update the optimal approach to limiting the adverse effects of statins while simultaneously optimizing the benefits of statin therapy. Although many adverse effects have been attributed to statin therapy, there are only 2 observed statin adverse effects in randomized, placebo controlled clinical trials: myalgias and glucose intolerance.4,5 The magnitude of these adverse effects is dependent on the dose and type of statin prescribed and the blood level of circulating statin concentration achieved. Therefore, using the lowest dose possible that still achieves the LDL desired goal should be the underlying strategy for all caregivers.

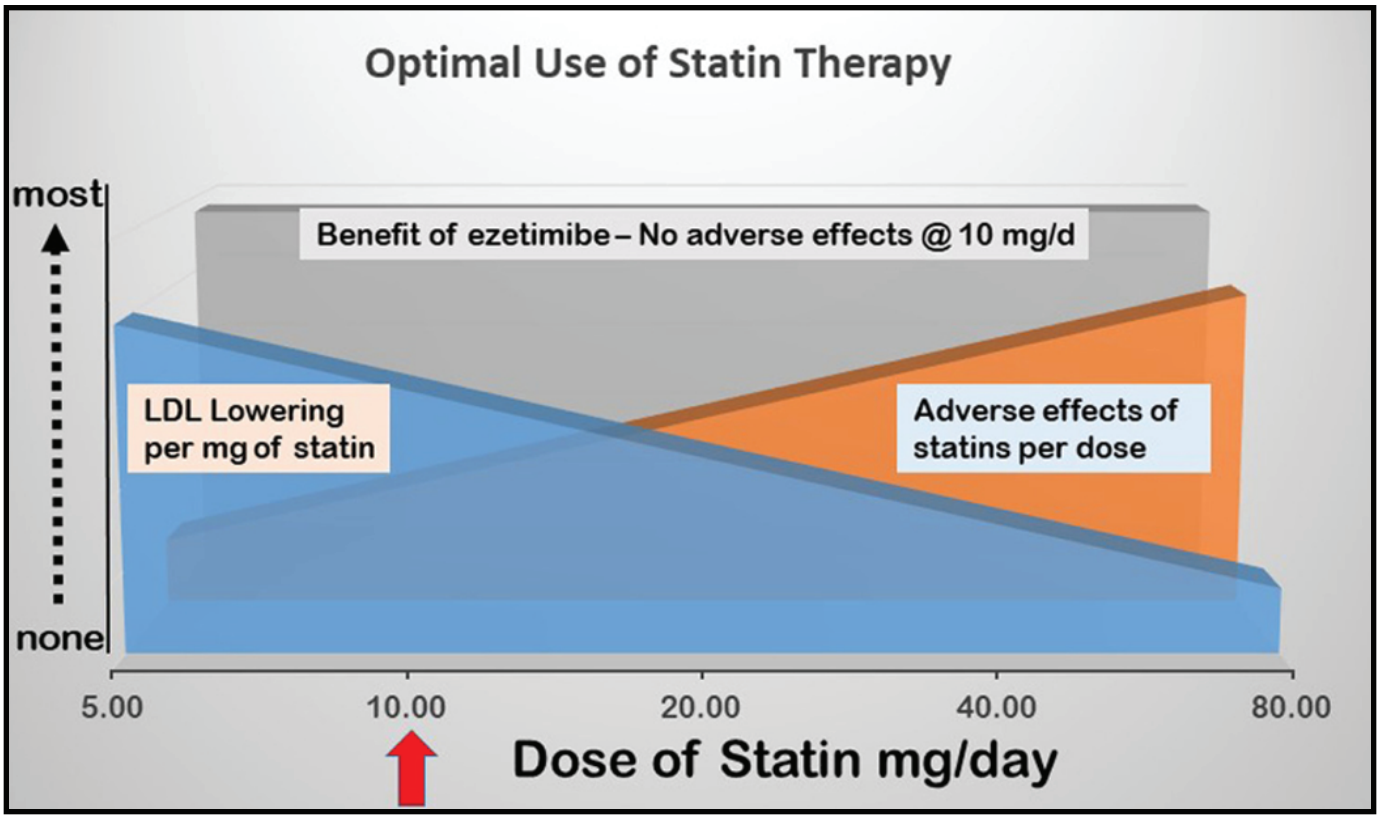
Optimal Prescribing of Statins to Reduce Cardiovascular Disease

Understanding the various metabolic effects of statins results in their correct use. When statins inhibit the synthesis of cholesterol at the liver, the hepatic content of cholesterol diminishes. This condition results in the activation of several lipogenic genes, resulting in an increase in the uptake of LDL cholesterol from the circulation via increasing the number of hepatic cell surface LDL receptors.6 What is under-appreciated are the other 2 gene-induced effects to increase hepatic cholesterol content by increasing the intestinal absorption of cholesterol and increasing the hepatic reuptake of cholesterol from the bile.6 Understanding this response can be effectively utilized clinically to optimize statin therapy. One important question is "Which statin should be prescribed?" Because all statins are available in generic formulation, cost is usually not a prime consideration. Most important is LDL cholesterol-lowering potency vs potential adverse drug–drug interactions and direct adverse effects (myalgia and diabetes). Considering these parameters, rosuvastatin has several advantages not shared with several other statins (eg, atorvastatin). When some statins are metabolized in the liver, the common enzyme cytochrome P4503A4 is activated but may also be simultaneously functioning to metabolize other drugs. P4503A4 catalyzes more than 50% of clinically used drugs. Rosuvastatin has the advantage that it is 90% excreted metabolically unchanged (primarily in the bile) so that minimal drug–drug interactions occur.7 In addition, rosuvastatin is the most potent of available statins such that 10 mg/d provides the same LDL reduction as 40 mg/d of atorvastatin.8 When rosuvastatin was directly compared with atorvastatin, simvastatin, and pravastatin at all available dosages in a randomized controlled trial, rosuvastatin was superior to all other statins in lowering LDL cholesterol.8,9 Because rosuvastatin is a very potent statin in lowering LDL cholesterol, it is possible to utilize a low dose of this drug (10 mg/d) to achieve a very significant reduction in LDL cholesterol (approximately 40%). In addition, rosuvastatin at a dose of 10 mg/d does not increase the risk of diabetes.10 All statins can induce myalgia and, in high plasma concentration, may cause rhabdomyolysis. However, the majority of myalgia complaints cannot be duplicated when the patient is blinded to the drug vs placebo.11 True statin-induced myalgia is dose related, and maintaining the statin dose as low as possible will minimize this adverse effect.

In order to obtain the maximal benefit of a statin, 2 of statins' gene-induced activities should be suppressed (the increase in cholesterol gut absorption and the reuptake of cholesterol from the bile). Both activities involve the cholesterol tissue receptor, which was identified in 1999 as the Nieman-Pick C1-Like 1 receptor. In the intestine, this receptor is specifically responsible for the uptake of dietary sterols, including cholesterol. Other sterols (particularly from plants, which do not synthesize cholesterol) are also transported by this receptor but subsequently are secreted back into the intestinal lumen for excretion. Fortunately, 50% of dietary cholesterol can be directly blocked with the concurrent prescribing of ezetimibe 10 mg/d. This receptor is also on the biliary duct endothelium of the liver, and its blockage prevents the liver from re-uptaking cholesterol from the bile. The addition of this generic medication results in an approximate 18% further lowering of LDL cholesterol.12 A recent, randomized clinical trial demonstrated that 10 mg/d of both rosuvastatin plus ezetimibe was superior to 20 mg/d of rosuvastatin in lowering LDL cholesterol and causing significantly fewer adverse effects.3

The other main beneficial effect of statins is their anti-inflammatory effect. A common approach to measuring the degree of inflammation is the level of C-reactive protein. Statins' reduction of inflammation is responsible for many of the beneficial effects of statins in acute coronary syndromes. There are no studies available that compare the anti-inflammatory effects of the available statins, nor are there comparative dose response studies. However, to date, all available statins have demonstrated anti-inflammatory effects, although rosuvastatin 20 mg/d is more effective than atorvastatin 40 mg/d at lowering C-reactive protein.13 In particular, rosuvastatin has demonstrated rapid-onset anti-inflammatory effects in acute coronary syndromes.14 In fact, addition of ezetimibe to rosuvastatin enhances the total anti-inflammatory effects.15

In summary, physicians should optimize the use of statins by considering the fact that the adverse effects are dose related, but the potency in lowering LDL cholesterol is not (Figure). In addition, statins, which don't compete with the metabolism of other medications, should be utilized. Based on physiology, in the majority of "at risk" patients, 10 mg of rosuvastatin plus 10 mg/d of ezetimibe are a logical initial choice to optimize statin use.



Optimizing statin therapy for primary preventionof cardiovascular disease in type 2 diabetes mellitus patients: Exploring dose, class, and intensity

Introduction

In 2021, the International Diabetes Federation Atlas reported that approximately 537 million adults worldwide had diabetes.1 In 2022, the Centers for Disease Control and Prevention's Diabetes Surveillance System estimated that about 11.3% of adults, equivalent to 37.3 million people, had diabetes, with 8.5 million remaining undiagnosed. Of this population, 95% had type 2 diabetes (T2DM).2,3 Patients with overt diabetes face an increased risk of cardiovascular disease (CVD), which is linked to the severity of hyperglycemia.4 Numerous studies, including a metaanalysis of 13 cohort studies, demonstrate this link.4 Even after accounting for factors like age, hypertension, smoking, hypercholesterolemia, and left ventricular hypertrophy, diabetes remains an independent CVD risk factor.5 In the context of primary prevention of CVD in T2DM patients, the rationale for reducing low-density lipoprotein cholesterol (LDL-C) is well-established. Observational and clinical trial evidence supports the idea that lower LDL-C levels reduce CVD risk. While clinical trials do not specify precise LDL-C targets, they do show that statin therapy can reduce relative CVD risk by approximately 30%.6 As the global T2DM population continues to grow, so does the associated CVD risk.1–5 Yet, no randomized controlled trial has explored the use of statins for primary CVD prevention in T2DM patients without prior CVD. Existing studies on primary CVD prevention with statins have yielded mixed results, with little focus on T2DM patients.7 Thus, additional epidemiological evidence is essential to assess the impact of statin dose, class, and use intensity in primary CVD prevention for T2DM patients. Our study aims to address this gap by utilizing realworld data to estimate the effects of statin dose, class, and use intensity on the primary prevention of CVD in T2DM patients without prior CVD.

Methods

Study population We conducted a population-based cohort study using data from Taiwan's National Health Insurance Research Database (NHIRD), which includes comprehensive medical claims, demographics, and vital status information.8 The study focused on patients with type 2 diabetes (T2DM) aged ≥40 from 2008 to 2020, excluding those with missing age data and those who switched statin classes during the follow-up period (1). Statin users were defined as those prescribed statins for >1 month annually, with a mean dose of ≥28 cumulative defined daily doses (cDDDs).8 The observation period extended until CVD occurrence, death, or December 31, 2021.8 Study covariates To adjust for potential confounders, patients were categorized into age groups, and analyses adjusted for age, sex, income, urbanization, types of antidiabetic drugs, diabetic severity, comorbidities, smoking, alcoholic liver diseases, and Charlson comorbidity index scores using inverse probability treatment-weighted (IPTW) Cox regression models (Supplemental Table 1).9 Comorbidity data were extracted from medical records within 1 year before the index date.9

Exposure to statins Statin exposure was coded using the Anatomical Therapeutic Chemical (ATC) classification system.10 Lipophilic and hydrophilic statins were analyzed as major exposures, and the intensity of statin use was based on average daily doses.10 Statistical analysis Time-dependent Cox hazard models were used to compare CVD risk between statin users and nonusers, and the study considered statin prescriptions every 3 months to define user status as a time-dependent variable. The study examined the effect of various statins on CVD risk and performed subgroup analyses with similar results. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Among patients diagnosed with T2DM between 2008 and 2020, our analysis encompassed 187,702 individuals, with an equal split between statin users and nonusers (93,851 each). The average age at T2DM diagnosis was 52.00 years for both groups. Notably, atorvastatin was the most commonly prescribed statin (33.29%), followed by simvastatin (21.59%) and rosuvastatin (17.13%) (Supplemental Table 1). Post-matching, absolute standardized mean differences (ASMD) for all baseline covariates were below 0.1 after using IPTW, indicating balanced covariates between statin users and nonusers. In terms of the association with CVD, 38,757 statin nonusers (41.30%) and 27,867 statin users (29.69%) developed CVD, with an adjusted hazard ratio (aHR) for statin users of 0.39 (95% CI = 0.38–0.39). Notably, various statins displayed significantly reduced risks of CVD among statin users, with aHRs ranging from 0.06 to 0.71 (Supplemental Table 2). The log-rank test showed significant differences in CVD risk between users of different statin classes (Figure 1). Furthermore, the intensity of statin use was explored, revealing a correlation between higher daily statin doses and reduced CVD risk (Supplemental Figure 2–3). Sensitivity analyses and incidence rate ratios (IRRs) confirmed the robustness of these findings (Supplemental Table 3). Overall, the IRR of CVD risk for statin users compared to nonusers was 0.56 (95% CI = 0.55–0.57), with variations observed among different statins and cDDD-year quartiles (Table 1).

Discussion

In this comprehensive study, we undertook the most extensive and long-term analysis of its kind, covering a mean follow-up duration of 9 years. Our findings unequivocally support the protective effects of statin use against the primary prevention of CVD in individuals with T2DM. Importantly, this study stands out as the first to explore the impact of different classes of statins on CVD prevention, offering a hierarchy of their effects in this patient population: pitavastatin > rosuvastatin > pravastatin > atorvastatin > simvastatin > fluvastatin > lovastatin. This hierarchy aligns closely with the known potency of these statins in terms of lipid profile improvements, including their effects on LDL-C, HDL-C, and triglyceride levels. Prudent management of T2DM often necessitates multiple medications, making the potential for drug interactions a matter of concern. Statins that exhibit fewer drug interactions, such as pitavastatin and pravastatin, or those with potent lipid profile-improving effects, notably rosuvastatin, may be particularly well-suited for individuals with T2DM seeking to prevent CVD.11 Surprisingly, evidence regarding the effects of statin intensity has been relatively scarce. While one trial from 2018 found no significant difference between more- and less-intensive statin therapy based on LDL-C targets,12 our study indicates a correlation between higher statin intensity (defined by DDDs) and a greater reduction in CVD risk among T2DM patients. Nonetheless, due to limited data on patients prescribed higher doses, our analysis couldn’t definitively evaluate the protective effects of extremely high doses compared to other DDDs.

Another uncharted territory was the impact of cumulative doses of statins on primary CVD prevention in patients with T2DM. Our results pointed to a direct relationship, where higher cumulative doses (cDDD-year) of statin therapy were associated with a lower risk of CVD. While the magnitude of our study's strengths lies in its sizable sample size, offering reliable real-world evidence with long-term follow-up, several limitations should be acknowledged. Notably, our use of claims data prevented the analysis of individual blood and lipid profiles, limiting our ability to establish associations between lipid profile changes after statin initiation and CVD risk. Furthermore, potential unmeasured confounders could have influenced our findings, despite our efforts to mitigate bias through various analyses. Additionally, the lack of data on body mass index and other lifestyle factors at the index date hindered the assessment of their contributions to CVD incidence. Lastly, the majority of our study population comprised individuals of Han Chinese ethnicity, primarily Taiwanese residents, limiting the generalizability of our results to other ethnic groups and countries.

Conclusion

In patients with T2DM, our real-world evidence demonstrates that statin use yields a dose-, class-, and use intensity-dependent reduction in CVD risk, with Table 1. IR and IRRs for primary cardiovascular disease. Events Person-years IR (10,000 person-year) IRR 95% CI for IRR p value Statin use Non–statin users 38,757 546,152.8 709.64 Ref Stain users 27,867 700,827.1 397.63 0.56 (0.55, 0.57)

Key points

• Question: Any real-world evidence of the statin dose, class, and use intensity for the primary prevention of cardiovascular disease (CVD) in type 2 diabetes (T2DM)?

• Findings: Our real-world evidence indicated that persistent statin use can enhance the primary prevention of CVD in patients with T2DM. Higher cumulative dose per year of statin use was associated with a higher reduction of CVD risk in patients with T2DM (P <0.0001for trend Compared with statin nonusers, pitavastatin exerted the highest effect on the primary prevention of CVD, followed by rosuvastatin, pravastatin, atorvastatin, simvastatin, fluvastatin, and lovastatin. Furthermore, a higher intensity of the daily statin dose was associated with a lower CVD risk in patients with T2DM.

• Meaning: This is the first study to clarify the protective effects of the cumulative dose-dependent intensity of different classes of statins on CVD primary prevention among patients with T2DM.

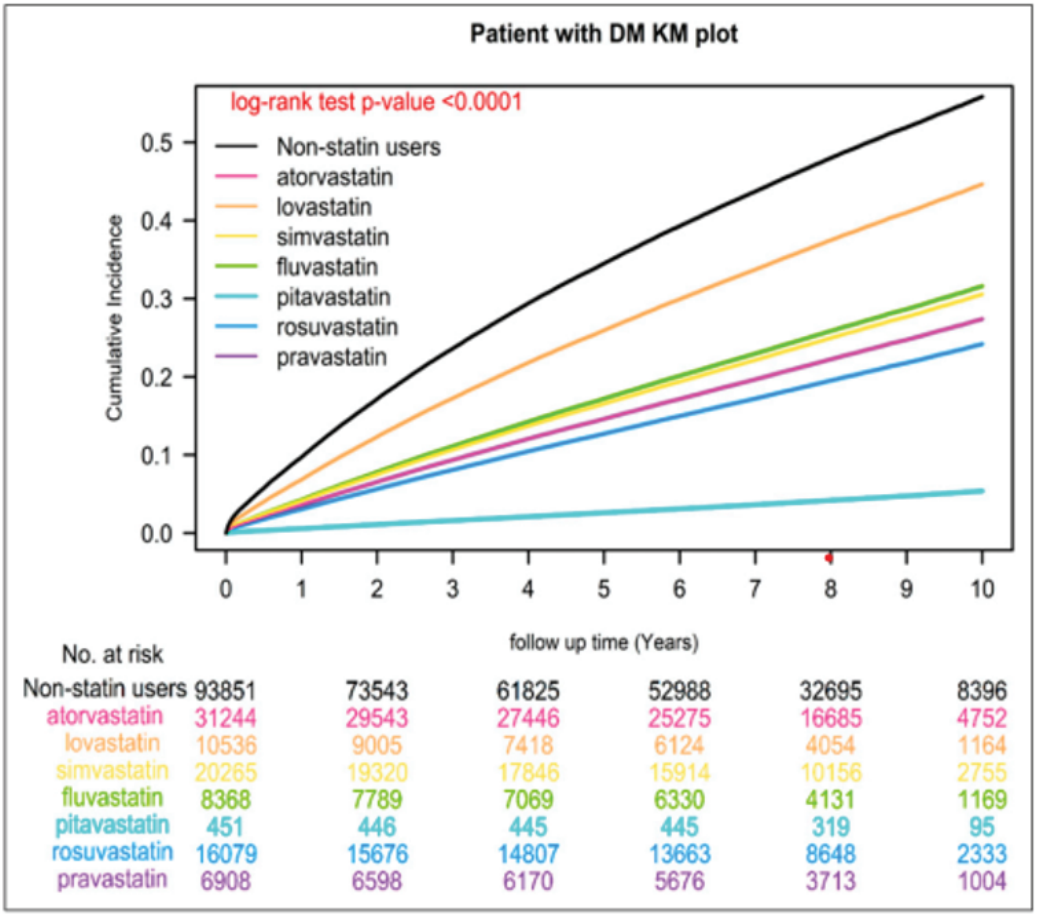


Figure 1. Kaplan–Meier of cumulative curves of primary cardiovascular disease for different classes of statins in patients with T2DM.

Table 1. IR and IRRs for primary cardiovascular disease.

	Events	Person-years	IR (10,000 person-year)	IRR	95% CI for IRR	*p* value
Statin use						
Non–statin users	38,757	546,152.8	709.64	Ref		
Stain users	27,867	700,827.1	397.63	0.56	(0.55, 0.57)	<0.0001
Classes of statins						
Non–statin users	38,757	546,152.8	709.64	**Ref**		
Atorvastatin	8,269	238,370.1	346.90	0.49	(0.48, 0.50)	<0.0001
Lovastatin	5,197	65,912.9	688.46	0.78	(0.68, 0.96)	0.0091
Simvastatin	6,200	152,088.4	407.66	0.57	(0.56, 0.59)	<0.0001
Fluvastatin	2,684	61,112.4	439.19	0.62	(0.6, 0.64)	<0.0001
Pitavastatin	15	3948.7	37.99	0.05	(0.03, 0.09)	<0.0001
Rosuvastatin	3,690	126,242.5	292.29	0.41	(0.4, 0.43)	<0.0001
Pravastatin	1,812	53,152.0	340.91	0.48	(0.46, 0.5)	<0.0001
Cumulative dose of statins (cDDD-year)						
Non–statin users	38,757	546,152.8	709.64	**Ref**		
Statin user dose, Q1	10,212	149,111.4	684.86	0.98	(0.94, 0.99)	0.0014
Statin user dose, Q2	8,460	165,785.3	510.30	0.73	(0.70, 0.74)	<0.0001
Statin user dose, Q3	5,933	185,196.1	320.36	0.46	(0.44, 0.46)	<0.0001
Statin user dose, Q4	3,262	200,734.3	162.50	0.23	(0.22, 0.24)	<0.0001

Abbreviations: DDD, defined daily dose; cDDD-year, cumulative defined daily doses per year; IR, incidence rate; IRR, incidence rate ratio; Ref., reference; CI, confidence interval; Q, Quartile.

The Challenge: Finding the Most Appropriate Statin and Dose for Each Patient

Introduction

Clinicians may believe that statin intolerance is "anything that the patient perceives it to be" because of the frequency and variety of patient-reported adverse events (AEs). The use of statin therapy is supported by decades of data demonstrating a reduction in morbidity and mortality with a safety profile similar to placebo.1,2 Yet unlike study subjects, clinic patients struggle with adhering to statins primarily due to muscle complaints or are skeptical to initiate statin therapy because of misconceptions, which may result in the nocebo effect (inverse of the placebo effect).3,4 Major societies provide formalized definitions of statin intolerance. The National Lipid Association (NLA) reports, "Statin intolerance is a clinical syndrome characterized by the inability to tolerate at least two statins: one at the lowest starting daily dose AND another at any daily dose, due to objectionable symptoms (real or perceived) or abnormal lab determinations, which are temporally related to statin treatment, and reversible upon statin discontinuation, but reproducible by rechallenge with other known determinants being excluded."5 Other cardiovascular (CV) societies specifically highlight the importance of drug-drug interactions (DDIs), conditions known to increase statin intolerance (eg, hypothyroidism, underlying muscle disease), and that symptoms must appear within the first 12 weeks of initiation or dose increase, with symptom improvement or disappearance within 4 weeks of discontinuing statin therapy. with guidance by major societies, identifying and managing statin intolerance, whether real or perceived, while finding the maximally tolerated statin and dose to maintain therapy continues to be a challenge for clinicians.

Discontinuing Or Not Optimizing Statin Therapy

LDL-C is considered the root cause of atherosclerosis.8 This relationship is supported by CV outcomes trials (CVOTs) dating back to 1984 with the Lipid Research Clinics Coronary Primary Prevention Trial, which utilized cholestyramine. A host of other CVOTs have demonstrated that a reduction in LDL-C, whether using ileal bypass surgery, statins, ezetimibe, or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors,10-13 results in fewer CV events. Finally, CVOTs, such as the Cholesterol Treatment Trialists (CTT) study in patients at low risk of a CV event, conclude that lowering LDL-C by 1 mmol/L (39 mg/dL) lowers CV risk by 23%.2 Lipidologists may argue that ignoring LDL-C is comparable to not acknowledging elevated blood pressure given the vast evidence from CVOTs,14 which is further supported by accumulating data indicating that non-adherence to statin therapy is strongly associated with higher rates of CV morbidity and mortality.15,16 Consequently, long-term use of statin therapy at the maximally tolerated dose in eligible patients is a key approach for reducing CV risk. Because the pharmacology of statins varies within the class, it is critical to properly select the most appropriate statin and dose based on individual patient characteristics.). These guidelines provide an in-depth discussion of risk stratification and appropriate therapeutic interventions.

The guidelines also updated the utility of coronary artery calcium scoring to assist in shared decision-making about initiating statin therapy. Long-term use of statin therapy can be a challenge often as a result of patient and clinician misperceptions. Once the seed of concern about a statin is planted, it can quickly become the clinical syndrome of statin intolerance as described by the NLA.18 Further, having to initiate non-statin therapies for LDL-C reduction is associated with prescribing complexities and additional time-consuming hurdles, limited efficacy, and often higher treatment costs.19 For example, ezetimibe is a safe and effective LDL-C-lowering agent that is generically available but has a relatively limited LDL-C reduction of ~20%. Bile acid resins have a similar limited effect on LDL-C, must be administered 1 hour before or 4 hours after other medications to prevent binding of concomitant agents, and are further limited by poor palatability and gastrointestinal (GI) AEs.14 Bempedoic acid is a new statin alternative that lowers LDL-C by ~20%, but often requires prior approval by many third-party payers. Moreover, its impact on CV events has yet to be determined.20 Finally, PCSK9 inhibitors are highly effective, possess a good safety profile, and have demonstrated CV event reduction in CVOTs, but prescribing barriers due to cost and the need for subcutaneous injection can be problematic.19

Clinical Assessment—What We Have Learned

Identifying patients with true statin intolerance and differentiating true intolerance from the nocebo effect are critical for managing and maintaining therapy. To help evaluate statinassociated muscle symptoms (SAMS), a clinical index score has been developed to capture objective information given that the frequently used biomarker to assess myotoxicity, creatine kinase (CK), is nonspecific and not always associated with symptoms (TABLE 1). 18,21 The myalgia index closely follows the NLA's definition of statin intolerance and indicates whether the patient's symptoms are probable, possible, or unlikely to be statin-related.22 Assessing and acknowledging underlying muscle, arthralgia, and pain disorders present at baseline is also important to discuss with the patient. Otherwise, such complaints may be attributed to the newly prescribed statin. Further, ruling out common conditions that may mimic SAMS (eg, physical exertion, low serum vitamin D) is imperative.21 Other patient-reported AEs and alterations in laboratory values, although less common, are also clinically observed with statins.23 These include headache, GI disturbances, and elevations in hepatic transaminases, CK, or glycemic markers. Guidance is limited for less common statin-related AEs, but switching statins or reducing the dosage is clinically prudent. For concerns related to laboratory elevations, obtaining baseline values among patients at higher risk for such abnormalities (eg, people with prediabetes or nonalcoholic fatty liver disease) may be considered; otherwise the correlation to statin therapy will be unclear and may cause apprehension for both the patient and clinician. Marked elevations in hepatic transaminases are uncommon and dose-dependent, so if causation is linked to statin therapy, dosage reduction may be considered. A dose-dependent relationship also exists for statins and incident diabetes. Evidence suggests that atorvastatin, rosuvastatin, and simvastatin are more likely to worsen glycemic indices, while fluvastatin, lovastatin, pitavastatin, and pravastatin appear to have little or no effect.24-26 Preexisting risk factors for diabetes mellitus appear to play a role.27,28 Much has been learned regarding the risk factors for statinrelated myotoxicity since the first case reports of rhabdomyolysis involving lovastatin were published over 30 years age Severe myotoxicity is rare with statin therapy.14 However, case reports have identified critical DDIs and other factors that predispose patients to muscle-related AEs (TABLE 2). In addition to DDIs, key components commonly involved with severe myotoxicity include medical complexity and advanced age. Other common clinical traits involving SAMS include chronic kidney or hepatic disease, low body mass index (BMI), and underlying musculoskeletal or metabolic conditions.21

Statin therapy is associated with an extensive spectrum of muscle complaints, ranging from benign symptoms to rare cases of rhabdomyolysis.18 Thus, proper clinical assessment is important. However, emerging research demonstrates a strong connection to statins and the nocebo effect among most patients considered statin-intolerant.30,31 The nocebo (Latin for "I shall harm") effect can occur when a patient has negative treatment expectations that result in AEs even when the treatment is benign.4 Common scenarios may involve a negative statin news story or purported AEs in a family member, which cause a patient to note a worsening of muscle complaints with their statin or cause a candidate for statin therapy to hesitate in initiating treatment. Many patients will also commonly research medication adverse effects via the Internet; a recent Google search of "statin side effects" yielded more than 9.3 million results. Unfortunately, this may negatively impact patient care as statin adherence and CV events worsen upon patients' hearing a negative statin-related news story. Conversely, positive stories result in adherence and a reduction in CV events.32 Frequency of statin intolerance Rates of reported statin intolerance are highly variable and dependent upon the setting.33 Data from randomized controlled trials (RCTs) demonstrate discontinuation rates and AEs comparable to placebo. A meta-analysis of placebo-controlled RCTs (N > 125,000) with a mean follow-up of 4.1 years was conducted.34 Discontinuation rates for statin users (13.3%) and placebo recipients (13.9%) were not statistically different, nor were differences noted between primary and secondary prevention subgroups. Similar observations were reported for incidence of myopathy (muscle weakness + elevated CK) between treatment and placebo groups. These findings are in sharp contrast to the statin intolerance rate of 29% reported in clinical practice.6 Why is there such a gap between study subjects and patients in real-world clinical practice? Differences may be attributed to the study subjects being carefully selected and monitored and willing to begin treatment, which is often not the case for clinic patients.14,18 But it needn't be so. High tolerability among study subjects illustrates that avoidance of major DDIs and careful monitoring of clinic patients coupled with explicit counseling on the risks and benefits of statin therapy may result in improved adherence, fewer AEs, and improved clinical outcomes. Patient education during the shared decision-making process prior to statin initiation is critically important since recent findings strongly suggest that the nocebo effect is responsible for most cases of SAMS. Two trials specifically designed to test the nocebo effect among patients classified as statin-intolerant have been conducted. The SAMSON trial was a double-blind study that evaluated severity of SAMS among patients who previously discontinued statin therapy due to intolerable AEs.30 Subjects were given a total of 12 bottles, with 4 bottles containing atorvastatin 20 mg, 4 bottles containing matching placebo, and 4 empty bottles. Each bottle was used or 1-month periods in random sequence, with subjects reporting symptom intensity daily. No significant difference (P=0.39) in mean symptom scores (0=no symptoms; 100=worst imaginable symptoms) between placebo months and statin months was observed; and interestingly, subjects also reported symptom scores even during the no-tablet months. Similarly, the Statin Web-based Investigation of Side Effects (StatinWISE) study enrolled 200 subjects with a history of statin intolerance.31 Participants were provided atorvastatin 20 mg daily or placebo for 6 double-blind, 2-month treatment periods and asked to rate their muscle symptoms. Overall muscle symptom scores did not differ between the placebo and atorvastatin treatment periods. Also, study withdrawal because of intolerable muscle AEs was similar between groups. Most of the subjects completing the trial reported restarting long-term statin therapy.

Differences Among Statins

Muscle complaints with statin therapy are considered a class effect and RCTs evaluating SAMS with individual agents are limited to small trials.18 Nonetheless, insight regarding statin properties and communications from the US Food and Drug Administration (FDA) provide some prescribing guidance.35,36 Statins that undergo extensive cytochrome P450 (CYP) 3A4 metabolism include lovastatin, simvastatin, and, to a lesser extent, atorvastatin.35 Concomitantly administered inhibitors of CYP3A4 (TABLE 2) can cause a considerable increase in serum levels of these statins and resultant concentration-dependent AEs. Conversely, CYP metabolism, particularly CYP3A4, plays no/minimal role in the clearance of fluvastatin, pitavastatin, pravastatin, and rosuvastatin.35 Yet like all statins, these agents are implicated in DDIs with concomitant therapies (eg, cyclosporine, gemfibrozil) via other statin metabolic pathways.35 Data also indicate higher rates of SAMS with the more lipophilic statins.37,38 Agents such as atorvastatin, lovastatin, and simvastatin are considered lipophilic statins that may be more likely to diffuse into extrahepatic tissue (eg, skeletal muscle) than their hydrophilic counterparts (pravastatin, rosuvastatin). Finally, theories have been proposed regarding the role of coenzyme Q10 (CoQ10) and the development of SAMS.21 Statins typically lower serum levels of CoQ10, and deficiencies of CoQ10 are associated with AEs including myalgia. Theoretically, supplementation with CoQ10 should offset SAMs, or utilizing a statin (ie, pitavastatin) that does not lower serum CoQ10 may limit muscle complaints.21,39Clinical reports support both approaches, yet formal studies assessing the impact on SAMs are limited. Only small studies have evaluated possible differences between individual statins and SAMS. However, findings align with the aforementioned factors. Rosuvastatin has demonstrated favorable tolerability at lower daily doses and intermittent dosing (eg, 2-3 times/week).21 Pravastatin and fluvastatin, although less potent, appear to be alternatives when patients are unable to tolerate more-potent statins. Finally, 2 studies indicate that ~70% of patients can tolerate pitavastatin39,40 and remain on therapy for >12 months when previously reporting statin intolerance.40,41

Statin Optimization Strategies Case Scenario (Cont'd)

A review of the patient’s medication profile shows that he has taken verapamil and gemfibrozil for several years. Both are metabolic inhibitors that potentially elevated serum levels of his previous statins (atorvastatin, simvastatin) severalfold. This DDI would have caused concentration-dependent AEs resulting in his limited ability to climb steps. This case emphasizes the importance of choosing initial statin therapy carefully and/or modifying concomitant medications as appropriate to avoid major DDIs. Once patients experience SAMS, they frequently become hesitant to initiate or optimize statin therapy. Since the patient was receiving ezetimibe in combination with simvastatin, it, too, might be eliminated from future use because of perceived intolerance. Since the patient case likely illustrates valid SAMS, rechallenging with a noninteracting statin or finding alternative treatments to the interacting medications would be prudent. Counseling the patient that ezetimibe is not a statin and likely did not contribute to his AEs is also imperative. Ultimately, combining the ezetimibe with a statin free of major DDIs would likely be well tolerated and achieve significant LDL-C reduction, possibly avoiding the need for a PCSK9 inhibitor. True intolerance or nocebo effect? A key to optimizing statin therapy is differentiating true intolerance from the nocebo effect. Data support that most clinic patients reporting SAMS are experiencing the latter.30,31

Utilizing such tools as the NLA's Myalgia Clinical Index Score can help guide the practitioner.18 In our patient case, the reported symptoms, pattern, and timing associated with statin dechallenge and rechallenge reveal an index score of ~11, indicating a "probable" association. In contrast, those with the nocebo effect have lower index scores because of more-generalized complaints, nonspecific distribution, and timing of symptoms that do not align with the initiation and discontinuation of statin therapy. It is also important to note that most patients considered statin intolerant can tolerate some level of statin intensity Patient engagement and shared decision-making Engaging the patient and utilizing shared decision-making are critical for managing SAMS. Working through the clinical index score and illustrating to those with the nocebo effect that the reported symptoms do not align with their statin can be an effective strategy for reintroducing or optimizing therapy. Questioning the patient regarding how bothersome their reported AEs are and addressing any concerns or hesitations that may be present further engages and allows the patient to believe their input is part of the solution. Finally, educating the patient on the benefits of statin therapy, including significantly reducing their chances of a major catastrophic vascular event such as a myocardial infarction or stroke, is often very motivational in guiding their decision to initiate or continue statin therapy. The protective effects of statins are durable and consistent across databases, extending beyond 30 years.2,14 Strategies for continuing the statin despite intolerance Upon reintroduction of statin therapy or a dose increase, a few strategies can be considered to potentially elevate the statin threshold. Limited data suggest that repleting low serum vitamin D levels or initiating the ubiquinol formulation of CoQ10 may improve statin tolerability and/or possibly offset the nocebo effect.21,42 Although the data are limited, such therapies are safe and may be clinically justified if supplementation enables patients at high CV risk to receive statin therapy. Older data indicate that 43% of statin-intolerant patients experience no recurrent symptoms when simply switching statins.43 Yet a more guided approach may produce better results. Instead of randomly switching to another statin, practitioners should consider choosing agents with data supporting improved tolerability and probability of fewer DDIs, including rosuvastatin and pitavastatin. If less LDL-C reduction is needed, fluvastatin and pravastatin are alternatives.21,35,38 For patients who are highly statin-intolerant or hesitant to initiate therapy, using conservative, intermittent dosing with gradual titration can be effective. Statins possessing long half-lives (ie, atorvastatin, pitavastatin, rosuvastatin) can achieve significant LDL-C reduction when administered a few times weekly. The intermittent dosing also simplifies determining if an AE is statin related.21 For example, if the patient begins rosuvastatin 10 mg every Sunday and reports muscle complaints later in the week, the timing and pharmacokinetics do not support a correlation to the statin. This can be a key point when counseling patients. Ongoing assessment Continued monitoring and reassurance is often needed to maintain statin therapy, especially among patients who are highly statin-intolerant.21 Critical to success is educating those experiencing the nocebo effect that reported AEs are not likely statin-related. This may require periodic statin dechallenge and rechallenge for resistant patients. Clinical follow-up of statin-intolerant patients typically follows a few scenarios. First are those patients who are managed by switching to a better-tolerated statin and/or, when able, modifying concomitant medications to avoid subsequent DDIs.21 Such patients illustrate the importance of appropriately selecting an initial statin that avoids major DDIs and potential AEs for improved tolerability. For more-intolerant patients, a regimen of vitamin D and ubiquinol (CoQ10) may be considered (although evidence is controversial), followed by conservative and gradual titration of an extended-half-life statin.21 Many patients who are highly statin-intolerant can successfully utilize a low-dose, intermittent statin regimen with concomitant ezetimibe.

Such combination therapy has few third-party payer barriers and can often achieve an LDL-C reduction of ~30% to 40%.21 Importantly, titration for those able to tolerate statin therapy to the maximally tolerated dose is essential. A key message from clinical guidelines is to achieve and maintain the maximally tolerated statin and dose. Finally, <5% for the of patients deemed statin-intolerant,5 the utilization of non-statin therapies, including ezetimibe, bempedoic acid, and PCSK9 inhibitors, will need to be considered to achieve the required LDL-C reduction.

SUMMARY

Although no definition of statin intolerance has been universally adopted, many major organizations provide guidance to the clinician for identifying and managing statin intolerance. Nonadherence to statin therapy or not optimizing the statin dose is associated with a higher rate of CV events. It remains imperative to involve the patient in shared decision-making, explicitly counseling on the risks and benefits of statin therapy and common misconceptions that can result in statin hesitation or the nocebo effect. Certain statins are less prone to major DDIs and are likely better tolerated. Choosing such agents when reintroducing statin therapy and implementing other strategies are critical to prevent recurrent statin intolerance and ultimately improve long-term adherence and reduce CV events. The number one cause of death in the United States remains heart disease, and statin therapy is one of our core strategies in our ongoing attempts to mitigate this disease

Key Take Aways

Key points

- Discontinuing statin therapy results in increased cardiovascular risk.
- The nocebo effect is a common reason for perceived statin intolerance.
- Statin intolerance is much less commonly reported in clinical trials than in clinical practice, suggesting that patient education and other safeguards employed in clinical trials are important to include in clinical practice.
- Several strategies are available that can enable continuation of statin therapy in patients who are truly statin-intolerance

TABLE 2. **Clinical factors potentially predisposing to statin-associated muscle symptoms**[21]

Advanced age
Female gender
Asian ethnicity
Low body mass index (frailty)
Pre-existing muscle/joint/tendon conditions
Chronic pain disorders
Diabetes mellitus
Obesity
Neuromuscular conditions
Chronic renal or hepatic disease
Hypothyroidism
Vitamin D deficiency
Physical exertion
Family history of myalgia (with or without statin therapy)
DDIs via CYP3A4: potentially ↑↑ statin serum levels
Amiodarone
Azole antifungals - multiple agents
Amlodipine
Diltiazem
Verapamil
Macrolide antibiotics - clarithromycin, erythromycin
Protease inhibitors - multiple agents
Excess grapefruit/juice consumption
Other common interacting medications
Cyclosporine
Gemfibrozil

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