Clinical Burden of Statin Intolerance

The term statin tolerance is not well defined today despite the wide use in clinical practice and published literature. The European Atherosclerosis Society (EAS) and the American College of Cardiology (ACC) statin intolerance tool focuses solely on muscle-related symptoms. However, a wide range of systemic adverse effects of statins may also limit statin use. An individual experiencing muscle pain while on statin therapy does not conclusively lead to a diagnosis of statin intolerance. In the 2018 American Heart Association (AHA)/ACC guidelines for management of blood cholesterol, it was noted that within the document the term statin intolerance was replaced with the preferred term “statin-associated side effects,” because most patients are tolerant to a statin rechallenge with an alternative statin or dosing regimen. Although the debate continues to be ongoing, many practicing healthcare providers would consider statin intolerance to be a reason why an individual is unable to tolerate appropriate statin doses to achieve target low-density lipoprotein cholesterol (LDL-C) goals. As a result, there may be a discrepancy between physician diagnosis and utilization management criteria from managed care organizations (MCOs), which may define a statin-intolerant individual based on inclusion criteria of clinical studies (eg, muscle-related pain on 2 or more different statins).

The prevalence of statin-intolerant patients is estimated to be 10% to 15% of all individuals who take a statin. Statin use has continued to increase, and in 2011-2012 there were an estimated 38.7 million Americans on statin therapy, with a prevalence of 17.23% in the general population aged 20 years and older. Utilizing this prevalence and an approximate US population of 328 million in 2019, about 59.5 million people 20 years and older in the United States may have been on a statin. Using the previous estimates, this equates to approximately 8.9 million individuals who may be statin intolerant and represents a significant health concern. The consequences of statin intolerance may result in the inability to reach LDL-C goals, which can further result in clinical and economic costs.

In an observational study of one integrated health system from 2008 to 2014, patients with statin intolerance (n = 5190) were propensity-score matched to a control cohort (n = 15,570). At 24...
No months post follow-up, those in the statin-intolerant group had a higher rate (60%) of not reaching LDL-C goals compared with the matched control (45%) with an odds ratio of 1.85 (95% CI, 1.60-2.16). This corresponded with an increased risk of revascularization procedures (hazard ratio [HR], 1.66; 95% CI, 1.36-2.02), and no statistically significant increase in cardiovascular (CV) events (except death) with an HR of 1.14 (95% CI, 0.99-1.30). This suggests the need for an alternative pharmacologic agent to reduce the risk of revascularization procedures in patients who have a high risk of CV events and who are statin intolerant. An interesting observation from this study was that there was a lower risk of death in patients who had statin intolerance compared with the control group (HR, 0.54; 95% CI, 0.47-0.62). The authors suggest that this specific outcome may have been driven by institution-specific protocols that required those with statin intolerance to be on at least non-daily statin therapy with closer monitoring. This close monitoring may have led to earlier intervention prior to fatal events, higher healthcare utilization, and higher costs. Furthermore, this may be a contributing reason why patients with statin intolerance also incurred higher mean medical costs over this 24-month follow-up time of $8777 versus $7344 in the control group with a cost ratio of 1.2 (95% CI, 1.11-1.28).7

In another observational study of 952 patients from Hong Kong with stable coronary artery disease, study investigators noted that statin intolerance was an independent predictor of a major CV event (HR, 1.52; 95% CI, 1.06-2.19). Figure 1 illustrates the Kaplan-Meier curve that compared event-free survival of statin-intolerant individuals with those with no statin intolerance.8

The body of evidence in general supports that statin intolerance leads to increased clinical and economic burden potentially associated with increased medical costs.9 A significant number of patients who take a statin are statin intolerant and may benefit from additional pharmacologic agents to lower LDL-C to target goals. By not reaching target goals, the financial burden of hyperlipidemia and disease sequelae may adversely affect patients, MCOs, and health systems.

Cost of Hyperlipidemia and Complications

Increased healthcare utilization and costs associated with comorbid conditions drive increased costs in patients with hyperlipidemia. In 2014-2015, the estimated annual direct and indirect cost of CV disease and stroke in the United States totaled $351.3 billion, in which $213.8 billion amounted to direct medical costs. The largest driver of direct medical costs was hospital inpatient stays ($97.5 billion) followed by outpatient/provider visits ($46.6 billion), medication ($32.8 billion), home healthcare ($27.5 billion), and hospital emergency department visits ($9.4 billion). The overall cost of CV disease in the United States is expected to increase to an estimated $1.1 trillion annually by 2035.10

Several indirect costs are related to lost productivity from work. In one claims-based evaluation of Truven Health MarketScan Research Databases, 60,352 patients between the ages of 18 and 64 with hyperlipidemia were selected from 2002 to 2011. The results demonstrated in a cohort with individuals who experienced a CV event and related clinical procedures had significantly more hours lost during the first month of follow-up than those that qualified for workplace absenteeism (23.4 hours), short-term disability (51.7 hours) and those that qualified for both workplace absenteeism and short-term disability (56.3 hours) compared with patients without CV and related clinical procedures. Additionally, the event group was also associated with significantly higher costs in the first month, ranging from $683 to $1119. Authors noted that this difference narrowed as time continued.11

Another hidden cost of CV disease is informal caregiving, which has been defined as unpaid caregiving. This cost can include lost wages due to caregiving, home modifications, and other “invisible work.” It was estimated to be $61 billion in 2015 and projected to be $128 billion annually by 2035.12 Patients with hyperlipidemia represent a significant risk of developing CV disease and having an acute event.

![FIGURE 1. Kaplan-Meier Curve Comparing No Statin Intolerance to Statin Intolerance](image-url)
One large retrospective claims review of the Optum Research Database included adult patients with hyperlipidemia who had a CV event from 2006 to 2012. The sample population included 193,385 commercial insurance patients who met the inclusion criteria. At baseline (first qualifying CV event), total annual costs were $25,250 per patient. Patients were followed up to 3 years. Total annual cost of care was highest in the first year ($41,937) and declined over year 2 ($16,786) and year 3 ($15,133). A majority of this annual first-year cost (77%) was driven by acute inpatient medical costs within 30 days of the CV event ($22,404). It is important to note that this study was before the approval of PCSK9 inhibitors and therefore does not include this cost. Study investigators noted that costs were doubled in this population compared with a propensity-scored matched population with hyperlipidemia that did not experience a CV event.13 These findings were consistent with other previously published reports that demonstrated that annual costs increased after a CV event, especially in the first few years. In one study of 123,850 patients with hyperlipidemia, patients were divided into secondary prevention (n = 15,613), high-risk patients (n = 47,600), and primary prevention patients (n = 60,637). Patients in each cohort were included in the case group if they had a CV-related hospitalization due to either myocardial infarction, unstable angina, coronary artery bypass graft, percutaneous coronary intervention, ischemic stroke, transient ischemic attack, or heart failure after index date. This case group was propensity-score matched to a control group that had no CV-related hospitalizations. The total incremental cost, difference between all-cause total cost in the case group, and total cost in the matched cohort over 2 years was highest in the high-risk population ($20,003) followed by the secondary population ($19,320) and primary prevention population ($17,650). This study was conducted before the approval of PCSK9 inhibitors. It is important to note that despite the risk of CV events in all populations, utilization of any statin remained low in the secondary prevention (55.7%), high-risk (52.8%), and primary prevention (29.8%) populations.14 This may reflect a potential need for alternative LDL-C-lowering agents to achieve target goals.

In a retrospective analysis of a different claims database (IMS LifeLink PharMetrics Plus) from 2006 to 2012, patients with hyperlipidemia with a CV event were followed for 3 years to evaluate direct clinical and economic cost burden. A total of 267,165 patients were matched to a control cohort of 184,285 patients with hyperlipidemia without a CV event. Results were shown as incremental cost differences, which is the difference in costs between case population and the control cohort. The mean incremental cost difference between these groups was $39,869-$41,168 at 1 year, $5900-$9436 at 2 years, and $4704-$11,400 at 3 years for all risk cohorts. Similar to previous studies, investigators noted that the majority of cost in year 1 was due to acute hospitalization (incremental inpatient increase of 4.4-6.2 days) following the initial CV event, which ranged from $25,666 to $30,321 in direct incremental costs. This study reinforces that prevention of an initial CV event is a major contributor to reducing clinical and economic burden.15 Those with atherosclerotic cardiovascular disease (ASCVD) have also been linked to worsening health-related quality of life (HRQOL). In one Medical Expenditure Panel Survey study between 2006 and 2015 involving 20,131 individuals aged 40 years or older, the authors stratified HRQOL based on healthcare expenditure. A ratio of 20% to 40% was deemed as high financial burden and greater than 40% was classified as catastrophic expenditure. This ratio was based on a portion of annual out-of-pocket healthcare costs to post-subsistence (ie, food-related expenses) family income. Both high financial burden and catastrophic expenditure had significantly worse mean Short-Form-12 score (0-100, higher scores

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**FIGURE 2.** Relationship Between Healthcare Costs and Quality of Life Measures16

- **Poor Physical Quality of Life Score**
- **Poor Mental Quality of Life Score**
- **Fair/Poor Self-Reported Health Status**
- **High Psychologic Distress**
- **Risk for Depression**

<table>
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<tr>
<th>Risk-adjusted Odds Ratio</th>
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<tr>
<td>High Financial Burden</td>
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<tr>
<td>Catastrophic Healthcare Expenditure</td>
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*12-item Short-Form Physical Component Score in the lowest quartile.
*12-item Short-Form Mental Component Score in the lowest quartile.
*Self-reported health status of fair or poor (vs excellent/good).
*Kessler Index score ≥13.
*Patient Health Questionnaire 2 score ≥3.

correlate to better HRQOL compared with no financial burden (34.5, 32.9, 38.0, respectively). This difference was statistically and clinically significant. Additionally, both high financial burden and catastrophic expenditure populations had a higher risk of poor physical quality of life, mental quality of life, self-reported health status, high psychological distress, and risk for depression. These results are illustrated in Figure 2.16

The clinical and economic burden of hyperlipidemia and statin intolerance illustrates the need for additional pharmacologic agents to achieve LDL-C goals. While there are other nonstatin agents available such as ezetimibe, LDL-C reductions are modest and may not be sufficient to reach target LDL-C levels, especially in patients who are statin intolerant. With the approval of PCSK9 inhibitors alirocumab and evolocumab in 2015, healthcare providers have a potent agent that allows patients to reach LDL-C goals in addition to statins.3

Cost of PCSK9 Inhibitors

Since the approval of both alirocumab and evolocumab in 2015, there have been concerns regarding pricing and accessibility. Upon entry into the market, PCSK9 inhibitors faced scrutiny regarding the long-term clinical outcomes because the clinical efficacy showed a reduction in LDL-C but not in CV events. Additionally, many patients faced high out-of-pocket costs and challenges of receiving approval for therapy across MCOs. Regarding the differences in FDA-approved indications, both agents’ initial indications limited the scope of use to those on a maximally tolerated statin with heterozygous familial hypercholesterolemia or who have atherosclerotic disease who are not at LDL-C goals, and homozygous familial hypercholesterolemia (only for evolocumab).17 Since the initial approval, manufacturers have added the indication to use as an adjunct to diet alone or in combination with other lipid-lowering agents for treatment of primary hyperlipidemia and to reduce the risk of CV events in adults with established CV disease. This increased the eligible patient pool to include more of those at a risk of a primary CV event to any individual with hyperlipidemia who has not been able to reach target LDL-C. The Table summarizes the FDA-approved indications of PCSK9 inhibitors since initial approval.

Table: Indications of PCSK9 Inhibitors Since Approval18,19

<table>
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<tr>
<th>PCSK9 inhibitor</th>
<th>Initial indication(s)</th>
<th>Updated indication(s)</th>
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<tr>
<td><strong>Alirocumab</strong></td>
<td>Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD, who require additional lowering of LDL-C (July 2015)</td>
<td>To reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease (April 2019)</td>
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<tr>
<td><strong>Evolocumab</strong></td>
<td>Adjunct to diet and maximally tolerated statin therapy for treatment of adults with HeFH or clinical ASCVD, who require additional lowering of LDL-C (August 2015)</td>
<td>To reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease (December 2017)</td>
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**ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.**

It is important to note that the initial list price of PCSK9 inhibitors was greater than $14,000 and only included pivotal trial data. ICER went on to suggest that MCOs should consider prior authorization criteria to restrict use to those only on maximally tolerated statins, and those with a statin intolerance be re-tried on statins prior to use. Additionally, with the clinical evidence at that time, the price would have to decrease to $5404 to $7735 to be associated with long-term value to patients.20 Since this report was released, new clinical evidence has been published along with a lower list price for both agents. Along with this new evidence, updated ICER evaluations were also conducted.

**Alirocumab**

Beginning in March 2019, the manufacturer of alirocumab decreased the annual price to $5850.21 With this decreased pricing and newly published clinical data from the ODYSSEY trials, an updated ICER evaluation was completed. In patients with recent myocardial infarction and an initial LDL-C greater than or equal to 100 mg/dL, the annual price of alirocumab may be up to $7417 in order to achieve a threshold of $150,000 per quality-adjusted life-year (QALY). This demonstrated that alirocumab at the updated price may be cost-effective at a QALY threshold of $150,000 per QALY in the right patient population. It should be noted that this benefit is in addition to current best practices of statin therapy.22
Evolocumab
In December 2019, the manufacturer of evolocumab decreased the list price to $5850 annually to be on par with alirocumab. In patients with ASCVD, an LDL-C greater than or equal to 70 mg/dL, and current use of statin therapy, ICER's value benchmark price to achieve a $100,000 per QALY and $150,000 per QALY are $1725 and $2242, respectively. While the current annual cost did not meet the benchmark set forth by ICER, Fonarow et al conducted a cost-effectiveness analysis independent of ICER. This analysis demonstrated higher incremental costs of evolocumab, ranging from $3411 to $22,228 annually. This translated to a cost per QALY gained of $7667 to $56,655, depending on the risk level of the population. Data from the FOURIER clinical trial was utilized to determine the clinical benefit and cost-effectiveness. Fonarow concluded that evolocumab met the accepted cost-effectiveness industry thresholds in the population with very high-risk ASCVD.

Impact on Budget
After the initial approval of PCSK9 inhibitors, utilization continued to be low. One study including 3.6 million adults in the United States between July 2015 and March 2017 with either dyslipidemia, untreated LDL-C (≥130 mg/dL), or coronary artery disease/coronary heart disease illustrated only fewer than 1% of individuals were on a PCSK9 inhibitor while 54% received standard therapy. This study was conducted before the FDA updated indications for both PCSK9 inhibitors to include treatment of primary hyperlipidemia to reduce LDL-C. This indication was supported by trials such as FOURIER, which evaluated evolocumab in patients with established CV disease (prior myocardial infarction, stroke, or symptomatic peripheral artery disease, and on a statin therapy with LDL-C still ≥70 mg/dL). Based on the inclusion criteria from the FOURIER trial, one Canadian study estimated that approximately 2.7% of the general population and 51.9% of patients with ASCVD would be eligible for PCSK9 inhibitor use. Study investigators noted that regardless of the cost reduction associated with decreased events, utilization management should be used to limit use to those patients at higher risk who benefit the most to limit budget impact.

As an example, in a hypothetical sample population size of 1 million patient lives with the estimates previously described, approximately 27,000 individuals would be eligible for PCSK9 inhibitor use. With a list price of $5850 annually, this would amount to an increase of $13.16 per member per month if there were 100% adoption. However, this has not been the case. In a claims-based review of the Decision Resources Group database, study investigators observed that rates of PCSK9 inhibitor prior authorization approval rate and prescription volume did not increase with positive clinical data from the FOURIER and ODYSSEY trials. Improved access to these agents may depend on a combination of significant patient outcomes (eg, death, CV events) from future studies, appropriate utilization management, and appropriate pricing of these agents.

The Role of the Managed Care Pharmacist
Managed care pharmacists in coordination with healthcare providers can establish clinical programs to help increase adherence to statins. In a Cochrane review of 35 studies of interventions that improve adherence to lipid-lowering medication, investigators observed that “intensification of patient care” improved both short-term and long-term adherence as well as lowered total cholesterol and LDL-C. The types of interventions in these studies included electronic reminders, pharmacist initiatives, and professional education to help remember to take medications. MCOs can continue to work with these health systems to incentivize programs that provide team-based intensification of care. These initiatives can help with not only MCO adherence goals, but also optimization of LDL-C-lowering agents that can potentially decrease the unnecessary need for additional agents.

As evidence has illustrated, adoption of PCSK9 inhibitors has been slow and limited. Healthcare providers and pharmacists can agree that while this drug class has shown the clinical benefit in patients with hyperlipidemia, barriers to access that include prior authorization (PA) criteria and high out-of-pocket costs may result in limited utilization. With the recent price reductions in both commercially available PCSK9 inhibitors and updated clinical studies, newer cost-effectiveness evaluations have demonstrated at the price of $5850 annually, these agents are more in line with willingness-to-pay thresholds. While the cost-effectiveness and clinical benefit of these agents continue to be studied, managed care pharmacists should focus on appropriately managing utilization management tools to reflect FDA-approved indications and the population likely to benefit the most. This utilization management should seek to minimize time from PA submission to approval. The phrase that has often been used for this high-risk population is “time is plaque,” and reducing time to appropriate therapy should be a priority to decrease costly CV events. Pharmacists should also be aware of emerging novel therapy that could possibly affect this space such as inclisiran. This medication is a small interfering RNA to reduce LDL-C that is administered every 6 months for maintenance therapy. Whereas clinical trials support efficacy, a complete response letter was issued to the manufacturer to not approve by the “Prescription Drug User Fee Act (PDUFA) action date of December 23, 2020 due to unresolved facility inspection-related conditions.” Although not a PCSK9 inhibitor, this therapy would be in combination with statin therapy and would be a direct competitor to PCSK9 inhibitors. There are other PCSK9 inhibitors currently in development; however, no agents have a set PDUFA date for review.

Pharmacy benefit managers have previously established outcomes-based payment models with manufacturers with the intent of
improving affordability and accessibility with the ultimate goal of improving patient outcomes (eg, LDL-C goals).14,15 Other contracts may refund drug costs in the event of a heart attack or stroke.36 These contracts may require an MCO to lessen/remove utilization management and potentially prefer one PCSK9 inhibitor over the other to achieve this benefit. MCOs should ensure that cost-savings translate to the health plan if these contracts are established. This variety in PA criteria between MCOs may confuse providers and pharmacists and further complicate the PA process. For example, while one health plan may set PA criteria based on FDA labeling, some health plans may further restrict use to just one PCSK9 inhibitor or require additional paperwork to be processed (eg, required ezetimibe use in statin-intolerant patients, triglycerides ≤400 mg/dL). In an article published by Baum et al, one proposed solution involves implementing a single standardized PA form to streamline the process and decrease prescriber burden, especially for an indication as prevalent as hyperlipidemia.37

A potential medium to facilitate appropriate PA approval for PCSK9 inhibitors could be utilization of an integrated pharmacy service model in an outpatient clinic. In one study, a specialty pharmacy clinic was provided access to the electronic medical record of a health system and served as the point team to submit PAs and handle appeals. This study occurred between September 2015 and December 2016 and enrolled 299 patients prescribed a PCSK9 inhibitor. Of these patients, 57% had commercial insurance and 70% had an indication for ASCVD. Results showed that 96% of prescriptions resulted in access to a PCSK9 inhibitor. A majority (58%) were approved after the initial PA, and 29% were approved after an appeal. Approval took a median time of 8 days, and of those who were approved, 94% started therapy and 53% received financial assistance.38 Results from this study demonstrate that integrated pharmacist intervention in the PA process can significantly improve appropriate approval and access to PCSK9 inhibitors. This approval rate is significantly higher than a separate study that noted final approval rates for PCSK9 inhibitors to be 27.2% to 61.3% during this same time period.8,39 Health systems should consider utilizing outpatient pharmacy resources to increase appropriate access. It is worth noting that with the initial high annual price tag of nearly $14,000, PCSK9 inhibitors were designated as specialty medications and therefore limited to being dispensed from specialty pharmacy networks only. Due to the decrease in costs, many health plans and payers changed the designation of these products from specialty to non-specialty drugs. As a result, PCSK9 inhibitors shifted to being available at retail and community pharmacies. In the current landscape spanning several large payers, it is generally not a requirement to obtain PCSK9 inhibitors at a specialty pharmacy.

Conclusions

Although hyperlipidemia remains a major health concern, statin use may not be optimal either due to low adherence or statin intolerance. The definition of statin intolerance remains highly debatable. Some experts argue the definition should include only myopathy/myalgias, whereas others claim that an adverse reaction that limits use can be viewed as statin intolerance. Statin intolerance can affect up to 15% of all patients on statins and continues to pose a major health concern. Uncontrolled LDL-C and statin intolerance have been associated with serious CV events. Since approval of PCSK9 inhibitors in 2015, indications have expanded to include use in those on a maximally tolerated statin with heterozygous familial hypercholesterolemia or who have atherosclerotic disease who are not at LDL-C goals, as an adjunct to diet alone or in combination with other lipid-lowering agents for treatment of primary hyperlipidemia, and to reduce the risk of CV events in adults with established CV disease. Additionally, evolocumab is approved for use in homozygous familial hypercholesterolemia. After initial approval, utilization remained low possibly due to cost (list price > $14,000 annually) or restrictive coverage criteria. With the reduction in list price by 60% to $5850 annually and updated clinical outcome data, both alirocumab and evolocumab are more in line with the willingness-to-pay threshold. Going forward, managed care pharmacists can ensure coverage criteria are appropriately developed to give access to those who would benefit the most while decreasing barriers to access. Pharmacists are well positioned to collaborate with health systems to increase adherence to traditional LDL-C–lowering agents to decrease unnecessary usage of additional agents and to streamline PA processing to increase approval rates.

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REFERENCES