Current Gaps in LDL-C Lowering Therapy

Cardiovascular disease is estimated to be the cause of death for 695,000-800,000 people in the United States each year. (Million Hearts. 2021; CDC. 2023) Large clinical trials have also shown that reducing blood cholesterol, particularly by managing LDL-C levels, reduces future risk of CV disease. Statins are one of the most prescribed drugs in the country and are used to lower high levels of LDL-C. (Bai N. 2024) It is estimated that upwards of 40 million Americans are prescribed a statin. (Bai N. 2024) However, many patients taking statins are not meeting the 2022 ACC recommended levels of LDL-C, putting them at risk for future CV events such as coronary disease, high blood pressure, an MI, or even stroke. (Lloyd-Jones DM, Writing Committee. 2022)

There is a pertinent need to identify high-risk atherosclerotic vascular disease (ASCVD) patients and to prescribe them effective therapies to help lower LDL-C levels. The American Heart Association (AHA) recommends that all healthy adults aged 20 years or older have their cholesterol checked every four to six years. (AHA. 2024) The National Heart, Lung, and Blood Institute (NHBLI) recommends that cholesterol screenings should occur every 1-2 years for men aged 45-65 and for women aged 55-65. Additionally, people over the age of 65 should receive annual cholesterol tests. People with CVD or who have an elevated risk are recommended to get their cholesterol checked more frequently, but a timeframe isn't specified. Risk factors for CVD include a positive family history of heart disease, smoking, diabetes, obesity, high blood pressure, age, and sex. Risk calculators for both clinicians and patients, which can be useful in estimating ASCVD risk over 5-10 years are:

Risk calculator for patients (AHA):
https://professional.heart.org/en/guidelines-and-statements/prevent-calculator

Risk calculator for clinicians (ACC):
https://tools.acc.org/ldl/ascvd_risk_estimator/index.html#!/calulate/recommendation/

A recent analysis of US adults with commercial health insurance found that 55% of those with clinical ASCVD met the definition for very high risk. (An J, et al. 2020). Patients with very high risk ASCVD are defined as having multiple prior, major, ASCVD events or 1 prior major ASCVD event with multiple high-risk conditions as shown in figure 1.

Major ASCVD Events[1]
- Recent ACS (within past 12 months)
- History of prior MI or ischemic stroke
- Symptomatic PAD

High-risk Conditions
- Age ≥ 65 years
- HeFH
- Prior CABG or PCI
- History of HF
- Recurrent ASCVD events
- Major ASCVD event with ≥ 1 risk conditions
- Diabetes
- Hypertension
- Chronic kidney disease
- Current smoker
- LDL-C ≥100 mg/dL (2.6 mmol/L) despite maximally tolerated statin + ezetimibe

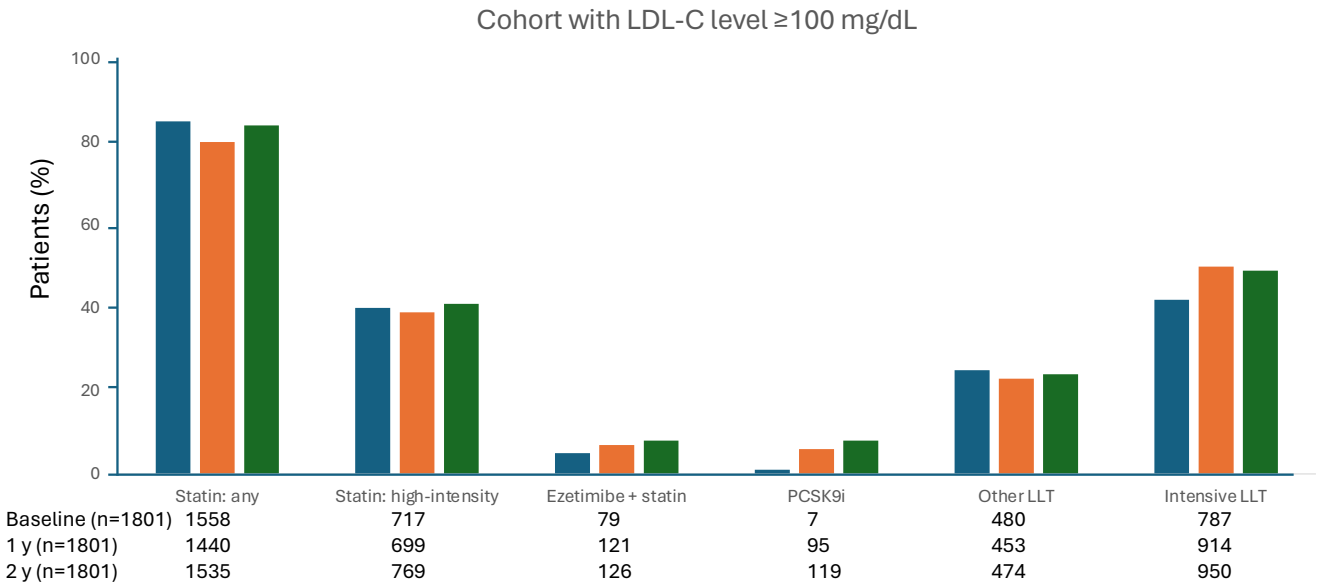
Among 27, 775 patients with a history of ASCVD in the MarketScan database as of January 1, 2016[2]
55.3% met the definition for very high risk and of those:
- 26.0% had major multiple ASCVD events
- 74.0% had a major ASCVD event and multiple high-risk conditions

1. Lloyd-Jones DM et al. *J Am Coll Cardiol.* 2022 DOI: 10.1016/j.jacc.2022.07.006
2. Colantonio LD, et al. *J Am Coll Cardiol.* 2019;74(20):2496-s507.

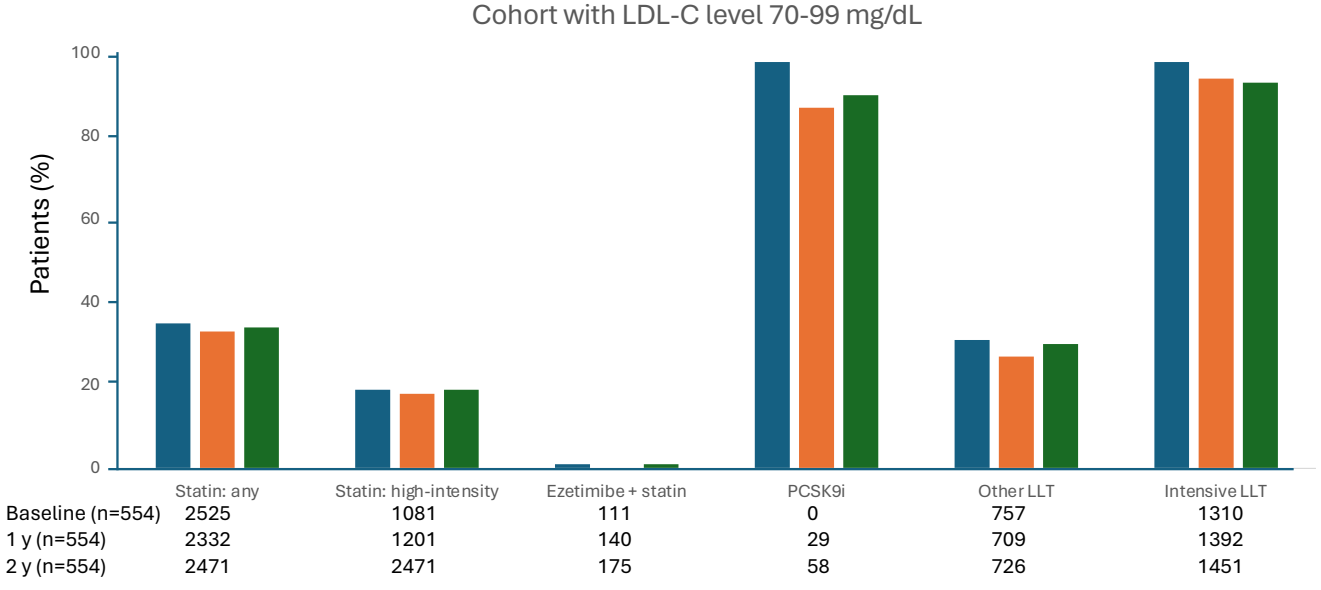
Figure 1. Criteria qualifying a patient as very-high risk for ASCVD. Slide adapted from Dr Taub's presentation at CMHC 2023.

The GOULD study examined LDL-C treatment patterns in patients in the US over 2 years and found that more African American and Hispanic patients had LDL-C levels higher than 100 mg/dL, despite being prescribed a statin and having high baseline use. (Cannon CP, et al. 2021) Additionally, over the 2 years only 17.1% of patients, across all ethnicities, experienced lipid-lowering therapy (LLT) intensification. The figures below show how patients' LLTs changed over the 2 years based on their LDL-C levels at baseline. The groups below were not taking a PCSK-9 inhibitor and were separated based on their LDL-C levels at the start of the study. Ezetimibe was added in 123 (6.8%) and 118 (4.5%) patients with LDL-C levels ≥100 mg/dL and for patients with LDL-C levels of 70-99 mg/dL, respectively. PCSK-9 inhibitors were added in 114 (6.3%) and 58 (2.2%) patients, respectively.

A



B



Figures 2A & B. Changes in LLT over 2 years in patients with LDL-C levels at the beginning of the study and either with levels ≥100 mg/dL or between 70-99 mg/dL. Cannon CP, et al. 2021.

The authors summarized their findings and noted that LDL-C levels did improve over the two years, but two-thirds of patients still had LDL-C levels ≥70 mg/dL indicating that patients still needed more intensive efforts to achieve optimal levels. Patients who were treated with PCSK-9 inhibitor therapies had a mean of ≤70 mg/dL of LDL-C and had higher adherence to their LLT. Authors also noted that the 2018 ACC guidelines were released during the study and that even with new guideline targets, LLT intensification did not change significantly. The 2022 ACC expert consensus decision pathway went even further and lowered the threshold for LDL-C target to 55 mg/dL for patients with clinical ASCVD or with very-high-risk ASCVD, or patients with a confirmation of familial hypercholesterolemia on high-intensity statin therapy. Thus, patients who are already at a high risk of ASCVD, need to be managed even more aggressively under new guideline LDL-C targets to reduce future risk of adverse CV events.

The attainment of a specific LDL-C target can be impacted by various factors, including the side effects associated with LLTs, patient compliance with LLT treatment, insufficient patient education, and the lack of regular monitoring by clinicians. Socioeconomic factors such as limited access to healthcare and the presence of comorbidities in addition to experiencing side effects are all factors which can impact patient adherence to LLT. It is hypothesized that socioeconomic factors contribute to early nonadherence and treatment side effects and polypharmacy contributes to later nonadherence. (Desai NR, et al. 2023)

One method to increase patient adherence to LLTs includes employing strategies such as training and educating patients, helping patients find financial assistance, and developing a collaborative relationship between provider and patient. Additionally, educating patients about their disease state and any new medications including dosing requirements, training them on how to administer injections and how frequently they must take their medications can also help improve adherence. (Desai NR, et al. 2023) Patient education is of importance as it helps "alter their health behaviors or improve their health status". (Delavar F, et al. 2020) Research has shown that following hospital discharge for a CV event, patients face problems with lifestyle management including maintaining a proper diet, physical activity, and taking medications as directed. Patient education for people with CVD has been shown to promote self-management behaviors and heart health, as well as improve patient satisfaction and health-related quality of life, reduce healthcare costs and hospital readmissions. (Niksadat N, et al. 2023) More frequent follow-ups between clinicians and patients can also help lead to achievement of LDL-C targets. A 2019 Italian study examined the effects of a touch point with patients at the beginning of the study and then again 3 months later. At the beginning of the study, patients with CVD had their LDL-C levels tested, and if they weren't meeting targets, had their medications adjusted. At the 3-month timepoint, LDL-C levels were again monitored. Results showed that initially, an estimated 23% of patients met LDL-C targets but after the 3-month monitoring period, this increased to 68.5% of patients meeting LDL-C targets. (Bosso G, et al. 2022)

It is pertinent to understand that if a high-dose statin is intolerable, reducing the dose, and adding a non-statin therapy may be a viable option for some patients. Additionally, even if patients are able to tolerate a high dose of a statin but still are unable to meet LDL-C targets, addition of a second therapy is likely going to be beneficial. Not only this, some patients may be in need of a third, additional therapy to help mitigate risk and meet lipid targets. (Lloyd-Jones DM, et al. 2022). Combination LLTs may be helpful when managing elevated LDL-C levels.

Clinicians need to be aware of the adverse events associated with statin intake and communicate these to patients ahead of time to prepare patients should they encounter any of the side effects. Statins may cause muscle symptoms and increase the risk of T2DM. The doses at which these side effects occur vary from statin to statin and from person to person. Statins, like other therapies, have a recommended dose range and myalgias and other side effects can be dose-dependent. There are a few risk factors for the development of statin-related myopathies which include: advanced age, the presence of renal or hepatic disease, female sex, and the use of certain concurrent medications. Additionally, signs of myopathies include muscle: cramping, soreness, fatigue, and weakness. (di Stasi SL, et al. 2010).

Newer, non-statin therapies include ezetimibe, PCSK-9 inhibitors, and bempedoic acid. Ezetimibe is one of the most prescribed non-statin therapies as it is an oral therapy, affordable, and generally well-tolerated. Additionally, dose adjustments generally aren't required for patients with hepatic or renal impairments. However, use of ezetimibe can cause GI side effects while PCSK-9 inhibitor therapies can be associated with injection-site reactions, flu-like symptoms, and nasopharyngitis. (Desai NR, et al. 2023)

Inclisiran, one of the newer PCSK-9 inhibitors, is administered as an initial, single subcutaneous injection, then again at 3 months, followed by injections every 6 months. This contrasts with evolocumab and alirocumab which can be administered subcutaneously every 2 weeks or monthly. Based on patient's preferences for self-injections, and the frequency of injections, clinicians can choose from the PCSK-9 arsenal to employ these therapies as add-ons for patients who still need assistance in meeting LDL-C targets. A new, oral, daily, PCSK-9 inhibitor is also in development, MK-0616. This drug is in Phase 3 trials currently, but it is hoped that it could offer another therapy option for patients who do not want to self-administer subcutaneous injections.

Practitioners need to balance patient health literacy, patient comfort with injections or daily oral administration, and tolerability of side effects in addition to helping patients meet LDL-C targets. Additionally, guidelines for cholesterol screening, and taking an in-depth personal and family history from patients is key for monitoring and tracking of disease risk over time.

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