FAMILY HEART FOUNDATION
Lipoprotein(a) & Familial Hypercholesterolemia

PRIORITIZING LDL-CHOLESTEROL CONTROL

To Stem The Rising Tide of Cardiovascular Disease in America:
Pragmatic Recommendations For Policy Makers, Payers, Practitioners, and Patients From The Family Heart Foundation

PRIORITIZING LDL-CHOLESTEROL CONTROL

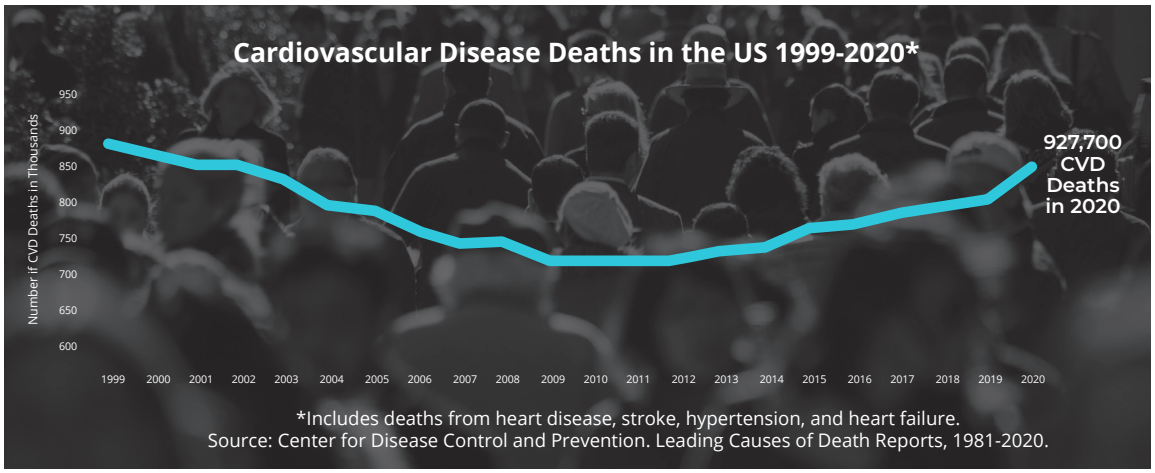
Analysis of Real-World Claims Database Reveals 72% of High-Risk Individuals Are Undertreated for Heart Attack and Stroke Prevention[1]

WHO WE ARE

The Family Heart Foundation is a nonprofit organization dedicated to saving lives from heart disease through research, advocacy, and education. The Family Heart Database™ contains diagnostic, medication, procedure, and lab result data on more than 324 million Americans. As part of our research efforts, we examine trends in treatment and outcomes of patients with high cholesterol to identify gaps in care.

SCOPE OF PROBLEM

Cardiovascular disease (CVD) is the leading cause of death and disease in the United States (US). During 1999-2011, CVD deaths declined, reflecting increased use of guideline-recommended medication and life-saving procedures. However, CVD deaths have been on the rise over the past decade and exceeded 927,700 in 2020, a substantial increase from approximately 874,600 in 2019. CVD places a large burden on the US health system at $403 billion annually, the majority of which stems from hospitalization costs.[2]



WHAT CAUSES CVD DEATHS

Fatty deposits (lipid-rich plaques) accumulate in the arteries during a person's life. Elevated low-density lipoprotein cholesterol (LDL-C) is a significant contributor to the development of atherosclerosis and CVD-related deaths.[2] Treatments that lower LDL-C have been proven to decrease the risk of heart attack and stroke.[3] However, patients with atherosclerotic CVD (ASCVD) or at high risk for ASCVD are not receiving adequate treatment for LDL-C reduction.

CALL TO ACTION

Barriers to the appropriate use of lipid-lowering therapies are putting lives at risk and adding to the economic burden of ASCVD in the US. All stakeholders—policymakers, physicians, health systems, patients, and payers—must take action to increase the percentage of patients who have controlled LDL-C to improve patient outcomes, reduce cardiovascular deaths, and lower healthcare costs.

FACTS & FIGURES

CARDIOVASCULAR DISEASE IN THE US

927,700 cardiovascular deaths in 2020[2]

$403 billion annual cost of CVD in US[2]

74 million Americans have elevated LDL-C[2]

~50%
PATIENTS with CVD are not taking LLT[13]

89%
PHYSICIANS SAY prior authorization requirements negatively impacted patient outcomes[28]

28%
PATIENTS know why they need to take medication[22]

FAMILY HEART DATABASE™ ANALYSIS[1]

38.1 million patients with ASCVD and/or elevated LDL-C

159 days the average duration of LDL-C control for patients who achieved LDL-C below guideline-recommended thresholds

72% patients had uncontrolled LDL-C

28% patients had controlled LDL-C

49%
HIGHER cardiovascular events for patients with LDL-C above thresholds

80%
OF PHYSICIANS don't prescribe combination therapy

PCSK9 INHIBITORS

91%
INITIAL COMMERCIAL PAYER REJECTION RATE for PCSK9 inhibitors[27]

74%
PATIENTS rejected for PCSK9 inhibitors do not take another LLT[27]

16%
INCREASE IN CARDIOVASCULAR EVENTS for patients denied PCSK9 inhibitors[24]

OVERVIEW

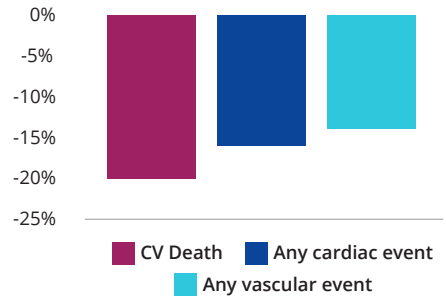
LDL-C is a modifiable risk factor for ASCVD. Reducing LDL-C lowers the risk of a major adverse cardiovascular event (MACE),[3] which can be fatal or life-threatening and is costly. MACE includes heart attack, stroke, and death. Reducing LDL-C levels is particularly important for someone who has had a heart attack, also known as a myocardial infarction (MI). Once someone has had an MI, the risk increases for another cardiac event.[4,5,6] Approximately one third of MIs each year are recurrent.[2]

Statins are effective at lowering LDL-C and MACE.[7] Research has shown that the degree of LDL-C reduction is correlated with fewer MACE. More-intensive statin treatment significantly decreases the occurrence of death, nonfatal MI, and ischemic stroke compared to less-intensive statin therapy. Every 1 mmol (~38 mg/dL) reduction in LDL-C decreases cardiovascular (CV) death by 20%, all cardiac events by 16%, and any vascular event by 14%.[3]

Statins are first-line therapy for most patients with elevated LDL-C levels. Statins are grouped into 3 categories by intensity: low, moderate, and high intensity. Low-intensity statins, which are generally prescribed to patients with low risk for ASCVD, reduce LDL-C by <30%. High-intensity statins, which medical guidelines recommend for patients with ASCVD or at very high risk for ASCVD, lower LDL-C by ≥50%.[7]

Statin therapy alone may not be sufficient to reduce LDL-C to acceptable levels. Combination therapy of a statin plus another lipid-lower therapy (LLT) is recommended for these patients. Ezetimibe, a nonstatin LLT which impedes dietary cholesterol absorption, can lower LDL-C by an incremental 13% to 20% when combined with a statin. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which are relatively new nonstatin LLTs, have potent lipid-lowering ability. When combined with a statin, PCSK9 inhibitors can reduce LDL-C by an incremental 43% to 64%.[7] Finally, bempedoic acid is an ACL inhibitor which inhibits cholesterol synthesis in the liver and reduces LDL-C by approximately 15% to 18% when added to a statin.[8]

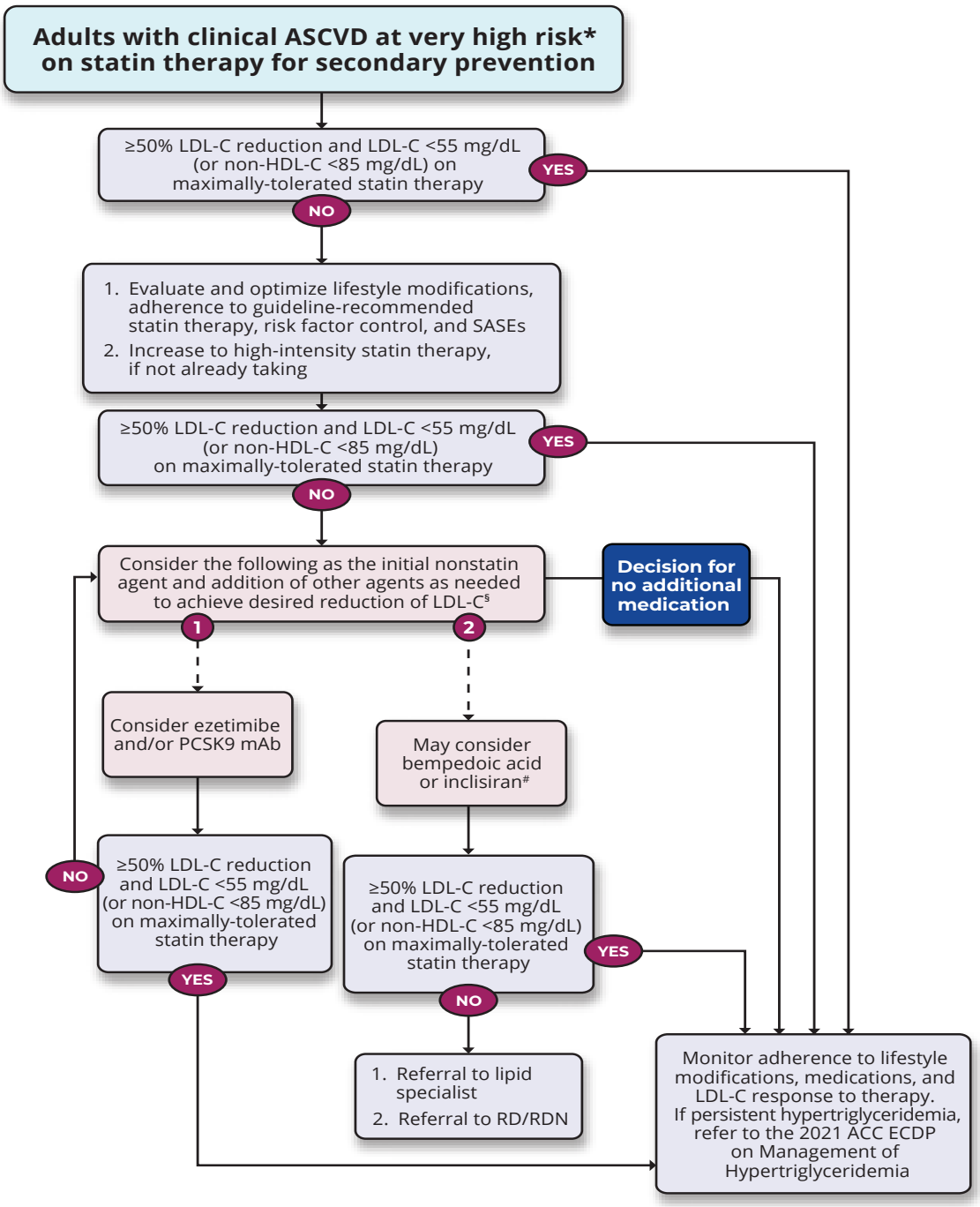
Intensive Lipid-Lowering Treatments Reduce Major Cardiovascular Events



PRINCIPLES OF LDL-C REDUCTION

The 2018 American Heart Association/American College of Cardiology Multi-Society Guideline on the Management of Blood Cholesterol recommends treating patients with clinical ASCVD with a high-intensity statin, with a goal of reducing LDL-C by at least 50%. The addition of nonstatin therapies are recommended for patients who have an LDL-C > 70mg/dL after statin therapy.[7] Additionally, the 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk recommended ≥50% LDL-C reduction and LDL-C < 55mg/dL for adults with clinical ASCVD at very high risk. Nonstatin therapies include ezetimibe, bempedoic acid, inclisiran, and PCSK9 inhibitors.[8]

AMERICAN COLLEGE OF CARDIOLOGY TREATMENT ALGORITHM FOR PATIENTS WITH ASCVD AND VERY HIGH RISK* ON STATIN THERAPY FOR SECONDARY PREVENTION



ACC—American College of Cardiology, ASCVD—atherosclerotic cardiovascular disease, HDL-C—high-density lipoprotein-cholesterol, LDL-C—low-density lipoprotein-cholesterol, PCSK9 mAb—proprotein convertase subtilisin/kexin 9 monoclonal antibody, RD/RDN—registered dietician/registered dietician nutritionist, SASE—statin-associated side effect.

*Very high risk includes recent acute coronary syndrome, history of myocardial infarction or stroke, symptomatic peripheral artery disease , age ≥ 65 years, heterozygous familial hypercholesterolemia, history of coronary revascularization, diabetes, hypertension, chronic kidney disease, current smoking, persistently elevated LDL-C (≥100 mg/dL while taking statin therapy plus ezetimibe, and history of congestive heart failure.

§For patients with clinical ASCVD and very high risk on statin therapy for secondary prevention who require >25% additional lowering of LDL-C, a PCSK9 inhibitor may be preferred as the initial nonstain therapy.

PCSK9 mAbs are preferred to inclisiran. If inclisiran is used, it should not be in combination with a PCSK9 mAb; it should be used instead of a PCSK9 mAb.

Source: Lloyd-Jones DM, et al. *J Am Coll Cardiol*. 2022; 80: 1366-1418.

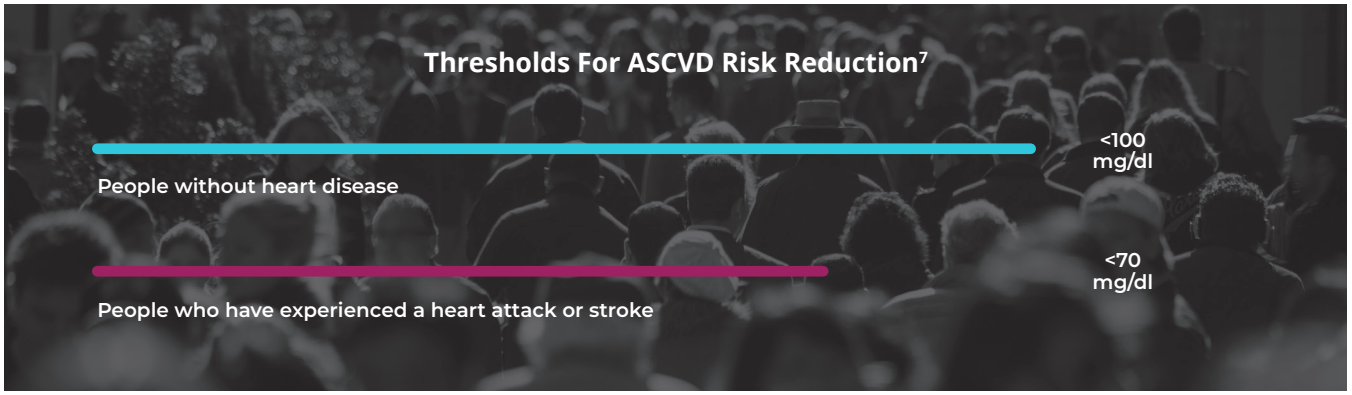
FAMILY HEART DATABASE™ ANALYSES

The Family Heart Database™ is comprised of real-world diagnostic, procedural, and prescription data from claims and/or laboratory information for >324 million individuals in the U.S. from 2012 to 2021.

The analysis was undertaken to examine the state of LDL-C control in individuals at increased risk for ASCVD and employed both qualitative and quantitative methodologies. The results of the quantitative analysis are presented below and insights from the qualitative research with healthcare practitioners and patients are incorporated into the *Recommendations* section.

The dataset used in the quantitative analysis included individuals in the Family Heart Database™ who were at risk for ASCVD or for a recurrent ASCVD event. Patients with severe hypercholesterolemia (LDL-C ≥190 mg/dL) are at risk for ASCVD, as are those with other risk factors for ASCVD and LDL-C >100 mg/dL. Individuals who met these criteria or who had ASCVD were identified. In addition, the database was examined to ascertain whether sufficient diagnostic, procedure, medication, and laboratory data were available to analyze LDL-C status and treatment patterns. There were 38,110,734 individuals within the Family Heart Database™ who met all criteria.[1]

Medical guidelines recommend clinicians speak to patients about initiation or intensification of LLT based on certain LDL-C thresholds. The threshold for individuals with severe hypercholesterolemia or other risk factors for ASCVD is LDL-C of >100 mg/dL. For patients with ASCVD, the LDL-C threshold is >70 mg/dL[7]. These thresholds were used in the analysis of the Family Heart Database™. Individuals were characterized as being Above Threshold, indicating excessive LDL-C levels, or Below Threshold, indicating adequate LDL-C control. The duration of LDL-C levels being above or below guideline-recommended thresholds was also recorded.[1]



LDL-C TREATMENT AND CONTROL RESULTS[1]

Over 27.5 million patients, representing 72% of the study population, were Above Threshold, signifying they did not achieve adequate LDL-C control. There were three patient groups that were Above Threshold:

- Those not taking any LLT
- Individuals taking a single LLT
- Patients taking multiple LLTs.

The largest group of patients with LDL-C above guideline-recommended thresholds were not taking any LLT, followed by individuals who were taking a single LLT. According to medical guidelines, these patients should have had a discussion with their physician about starting or intensifying LLT.

Duration of time above or below thresholds was also examined. LDL-C values change for a variety of reasons. Even patients who achieve LDL below guideline-recommended thresholds, the average duration of LDL-C control was 159.4 days, or less than 6 months.

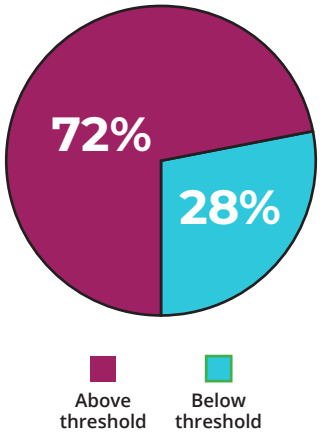
This analysis of a real-world claims database shows that 72% of people with ASCVD or at high risk for ASCVD had LDL-C levels above guideline-recommended thresholds, perpetuating risk for cardiovascular events.

It's unclear whether physicians failed to have these discussions with patients or if patients declined LLT. A sizeable percentage of individuals were taking a single LLT but continued to have elevated LDL-C. Based on the effectiveness of nonstatin LLTs, it's possible that the addition of another lipid reduction agent could have lowered LDL-C to below recommended thresholds. Only 20% of physicians prescribed combination LLT.

Our data on the undertreatment of high-risk individuals are in agreement with other studies. The GOULD registry enrolled 5006 patients with ASCVD in December 2016-July 2018. At two-year follow up, two-thirds of patients had LDL-C values >70 mg/dL. Over the study period, only 17% of patients had LLT intensification. Ezetimibe was added to treatment regimens in 6.8% of individuals with LDL-C >100 mg/dL; a PSCK9 inhibitor was added for 6.3% of these patients. These data were collected after the release of updated medical guidelines which recommended LLT intensification if LDL-C exceeded 70 mg/dL in patients with ASCVD. Thus, the GOULD registry provides evidence of clinical inertia related to adoption of standards of care.[9]

Aggarwal and colleagues examined the use of statins in adults with coronary artery disease (CAD) in the National Health and Nutrition Examination Survey (NHANES) data from January 2015 to March 2020. In this analysis, only 67.9% of these adults with CAD were prescribed a statin and 6.4% received ezetimibe. The majority of patients (73.5%) had LDL-C > 70 mg/dL. For those taking statin therapy, 65.2% had LDL-C above recommended threshholds.[10] In another analysis of NHANES, adult Americans averaged LDL-C of 111.7 mg/dL in 2017-2018, an improvement from 127.9 mg/dL in 1999-2000. The majority of patients with ASCVD (76.3%) had LDL-C ≥70 mg/dL in 2017-2018.[11] An analysis of a large administrative database of managed care health plans and Medicare supplemental health plans showed that 74.2% of people with ASCVD had LDL-C ≥70 mg/dL; the majority of these patients were not taking a statin or ezetimibe.[12]

LDL-C Levels and LLT use in the Family Heart Database™[1]



159
DAYS
Average duration of LDL-C control[1]

2/3
OF PATIENTS
with ASCVD have LDL-C above guideline-recommended thresholds[9]

Many ASCVD patients are not taking a statin or other LLT[1,9,11-13]

Undertreatment can reflect use of a low-intensity statin for patients with elevated LDL-C and/or high risk or failure to use combination LLT (a statin plus a nonstatin LLT). In the administrative database mentioned above, a scant 9.2% of patients with ASCVD and elevated LDL-C were treated according to medical guidelines with prescription of a high-intensity statin.[7,12] An analysis of >600,000 individuals with ASCVD in a large commercial health plan in 2019, approximately 50% of patients were not receiving any statin, and only 22.5% were appropriately treated with a high-intensity statin. Treatment was intensified in about 10% of patients. By type of ASCVD, 27.4% of patients with CAD and 22.0% of those with cerebrovascular disease were taking a high-intensity statin. Women were less likely than men to be prescribed any statin, including high-intensity formulations. Patient adherence to high-intensity statin therapy was encouraging at 82.8%.[13]

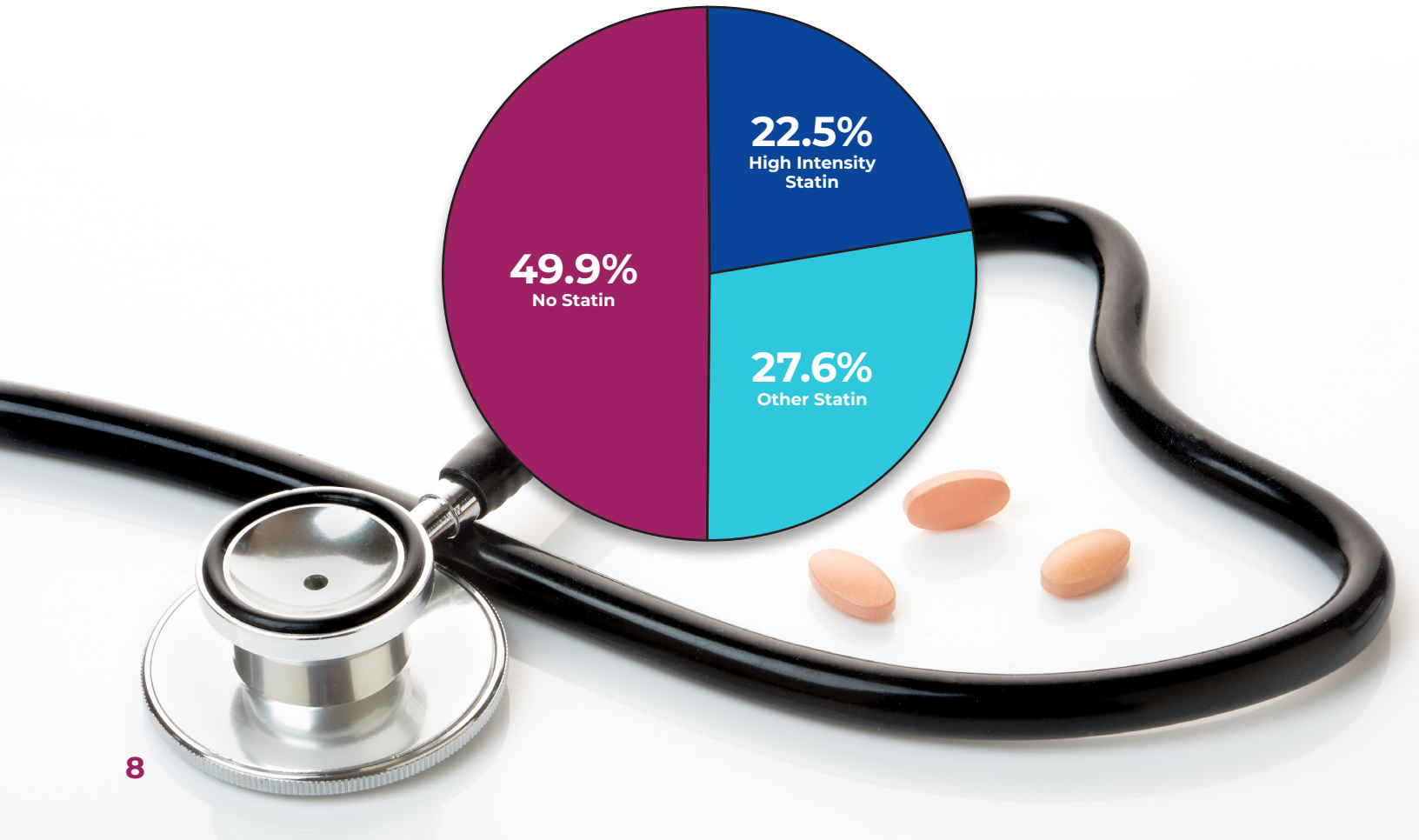
Our data on the use of add-on LLT is consistent with another recent analysis of the use of novel agents in patients with ASCVD. One study assessed the use of ezetimibe, PCSK9 inhibitors, and icosapent ethyl in individuals with ASCVD. Electronic health records at 89 US health systems during January 2018 to March 2021 identified 728,423 patients with ASCVD. Use of novel agents was low at 6% for ezetimibe, 1.6% for a PCSK9 inhibitor and for 1.3% icosapent ethyl.[14]

These data, taken together with our analysis from the Family Heart Database™, point to significant undertreatment of high-risk individuals with both statins and nonstatin therapies. Only a relatively small percentage of patients achieve or maintain an acceptable level of LDL-C.

The majority of patients have not had sufficient LDL-C reduction, putting them at unnecessary risk for heart attacks and other ASCVD events, including death.

STATIN USE AMONG PATIENTS WITH ASCVD IN A LARGE HEALTH PLAN

ASCVD - atherosclerotic cardiovascular disease Source: Data based on Nelson AJ, et al. *J Am Coll Cardiol.* 2022; 79: 1802-1813.



FAMILY HEART™ DATABASE: CONSEQUENCES OF FAILURE TO ACHIEVE LDL-C GUIDELINE THRESHOLDS IN PATIENTS AT ELEVATED RISK[1]

We assessed the consequences of failure to achieve LDL-C guideline threshold in patients at elevated risk using the Family Heart Database™. We identified individuals with severe hypercholesterolemia (≥190 mg/dL), other risk factors for ASCVD, or diagnosis of ASCVD who also met the following criteria:

- ≥48 months of sufficient diagnosis, procedure, prescription, and laboratory data
- ≥3 cholesterol laboratory results
- Were Above Threshold or Below Threshold at least 70% of the study period

LDL-C thresholds were defined by those established in medical guidelines:[7]

- ≥100 mg/dL for patients with severe hypercholesterolemia or other risk factors for ASCVD
- ≥70 mg/dL for individuals diagnosed with ASCVD

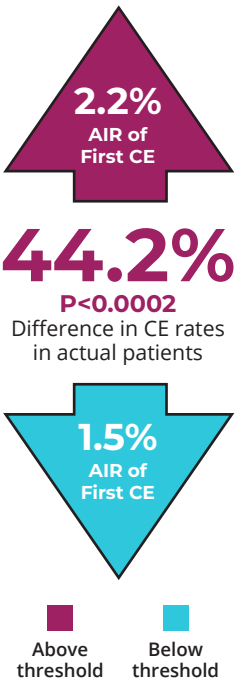
There were 56,349 individuals within the Family Heart™ Database who met these criteria—39,117 patients were Above Threshold and 17,232 were Below Threshold. Information was collected on LLT use, prescriptions filled, and LDL-C levels. An 18-month baseline period was used to ascertain covariates for propensity score matching. Thereafter, 2 propensity-matched groups were created, Above Threshold and Below Threshold, each with 14,755 patients.

Patients were then followed for ≥30 months to determine the first cardiovascular event and annualized incidence rate (AIR) of cardiovascular events.

- Individuals in the Above Threshold group had an AIR of first cardiac event (CE) 44.2% ($p<0.0002$) higher than those in the Below Threshold group (2.2% or 1,879 vs. 1.5% or 1,226).
- Total CEs (first and subsequent) in the Above Threshold group were also 49% higher ($p< 0.0002$) than those in the Below Threshold group (3,510 vs. 2,356).

This analysis of a real-world claims database demonstrates that high-risk patients who lower LDL-C levels to below guideline-recommended thresholds have a significant reduction in cardiovascular events. Greater emphasis on achieving LCL-C control would improve cardiovascular health at a population level.

Annualized Incidence Rate (AIR) Of First Cardiovascular Events



Source: Family Heart Foundation.

CHALLENGES TO EVIDENCED-BASED CARE

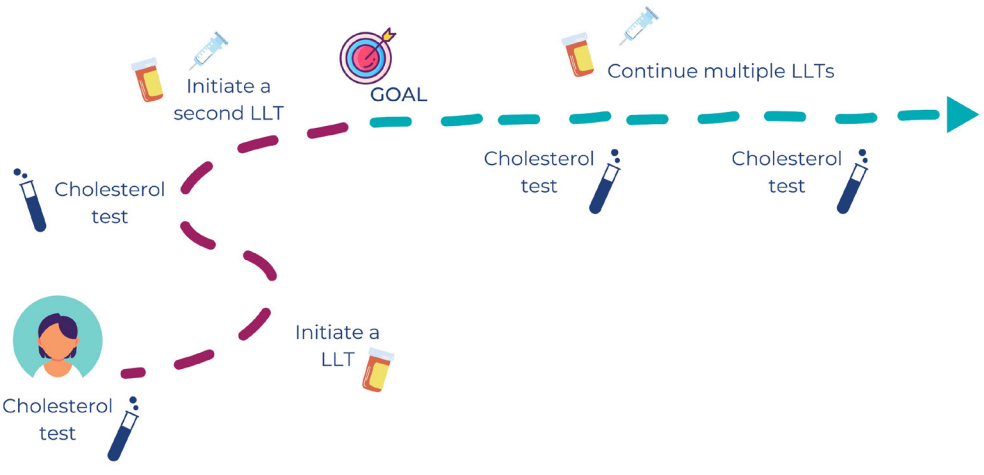
There are many barriers to LDL-C control, including factors related to clinicians, patients, and payers. These are discussed below, with recommendations for action on the part of policymakers, payers, clinicians, and payers presented later in this report.

CLINICIANS

A stepwise approach to lipid reduction is applied for most patients with elevated LDL-C levels. A statin is usually first prescribed and treatment is intensified, with a higher-intensity statin or add-on LLTs, until the LDL-C is below guideline-recommended thresholds.[7] However, in patients with very high LDL-C, use of a single LLT (statin monotherapy) is unlikely to result in LDL-C control. As a result, the International Lipid Expert Panel recommends combination therapy as first-line treatment in patients with very high risk for a CV event and elevated LDL-C.[15] The PL-ACS registry of patients with acute coronary syndrome (ACS) demonstrated the benefit of this approach. Patients taking combination therapy of a statin plus ezetimibe had significantly reduced all-cause mortality through three years compared to statin monotherapy.[16] Additionally, the RACING trial compared combination therapy of a moderate-intensity statin plus ezetimibe to a high-intensity statin in individuals with very high risk for ASCVD. Overall outcomes were similar between the groups but LDL-C control and tolerability were significantly better with the combination:[17]

- The primary outcome, which was a composite of cardiovascular death, major cardiovascular events, or nonfatal stroke within 3 years, was similar between groups at 9.1% for moderate-intensity statin plus ezetimibe and 9.9% for a high-intensity statin (p=0.43).
- A significantly greater percentage of patients taking combination therapy achieved LDL-C <70 mg/dL than those taking a high-intensity statin at 72% and 58%, respectively (p < 0.001).
- Discontinuation or dose reduction owing to adverse effects was lower for combination therapy than a high-intensity statin at 4.8% and 8.2%, respectively (p < 0.001).

PATIENT JOURNEY ON STEPWISE APPROACH TO LIPID REDUCTION



PERFORMANCE METRICS MATTER

Medical guidelines on blood cholesterol management issued in 2013 changed the way that HCPs approach lipid reduction. Previously, HCPs used a treat-to-target approach to identify the appropriate LDL-C value for patients. The 2013 guidelines introduced a new paradigm based on a patient's 10-year ASCVD risk, use of moderate- or high-intensity statins, and a targeted percentage reduction in LDL-C in four patient groups.[31]

Prior to the 2013 blood cholesterol guidelines, reduction of LDL-C was a national quality measure in the National Center for Quality Assurance-Healthcare Effectiveness Data and Information Set (NCQA-HEDIS). After release of the guidelines, LDL-C reduction was removed as a *performance* metric. Instead, the NCQA-HEDIS established a quality measure of percentage of patients who were prescribed a statin, which is *process* metric. Hypertension and diabetes continued to have performance, not process, quality metrics.[32]

These two events, removal of an LDL-C treat-to-target approach in medical guidelines and removal of LDL-C reduction as a performance metric, has had consequences. Most notably, physicians stopped routinely measuring LDL-C levels despite guideline recommendations.[32] In a survey of HCPs participating in the GOULD registry, 60% indicated they would *never* reassess LDL-C after initiation of statins.[33]

Research has shown that LDL-C measurement can help overcome clinical inertia and lead to an increase in LLT intensification. LDC-measurement also can improve patient adherence to treatment regimens.[32]

Clinical inertia, which is the failure to intensify treatment for a patient who has not reached recommended thresholds, is also a factor in the undertreatment of elevated LDL-C. As discussed earlier, there is ample evidence of LDL-C above guideline-recommended thresholds.[9-12] A survey of physicians revealed that clinicians often cite patient factors as the rationale for not prescribing a LLT to an individual with ASCVD or for failing to intensify treatment. However, the researchers concluded that lack of familiarity with medical guidelines was a factor in undertreatment of elevated LDL-C. In addition, clinicians were less likely to prescribe or intensify LLT in older patients and women.[18]

Failure to intensify LLT may reflect the busy schedules of healthcare providers (HCPs) who may not have the time needed to educate patients on the need for another statin or an add-on therapy. HCPs may also underestimate the benefit/risk of LLT and overestimate the potential side effects for some therapies (statins). This can lead to a lack the motivation to have discussions with patients, some of whom have misinformation about LLT, particularly statins. Risk calculators, such as the online ASCVD Risk Estimate+ and the app CardioSmart Heart Explorer created by the American College of Cardiology, may help physicians initiate these conversations.[19]

Technology has also been used in other ways to draw clinicians' attention to excessive LDL-C. One study found that sending physicians electronic "nudges" regarding patients' LDL-C levels and monthly comparisons of prescribing among peers more than doubled the percentage of patients placed on LLT. When combined with nudges to patients, the percentage of patients prescribed an LLT tripled.[20]

LDL-C OFTEN FALLS TO THE BOTTOM OF THE LIST OF CLINICIAN PRIORITIES BUT RECEIVING ELECTRONIC REMINDERS AND FEEDBACK ON WHAT OTHER PHYSICIANS ARE DOING CAN HELP OVERCOME INERTIA.[20]

PATIENTS

Patient adherence to statin therapy varies based on many factors, including the reason for LLT, understanding of why lipid reduction is needed, belief in physician and medication, ability to pay for medication, and socioeconomic factors, among others. A recent large study found that nearly 80% of people who had an MI were adherent to statin therapy in 2014, which compared to 67% of individuals with diabetes and 64% of people without MI or diabetes.[21]

Questionnaires sent to individuals enrolled in the GOULD registry revealed that the majority of patients didn't understand why there were prescribed an LLT. In addition, most did not know their risk for ASCVD or the degree of LDL-C reduction associated with their LLT. Only 28% of patients understood that taking an LLT would lower their risk for a heart attack or stroke. The majority of physicians in a related survey indicated that nonadherence primarily reflected patient belief that LLT did not work.[22]

In Family Heart Foundation interviews with patients, the lack of symptoms for high cholesterol translates to a lack of urgency to lower LDL-C. In addition, some patients believe LDL-C values can increase or decrease without a correlation to changes in diet, exercise, or medication, which means that patients may not take excessive LDL-C levels as seriously as they should.

These data points underscore the vital role of patient education in the reduction in ASCVD events and deaths.

The amount of co-pays for medication can also affect patient adherence to treatment plans. An analysis of studies evaluating the impact of patient cost-sharing on adherence found that 75% of studies showed that lower co-pays for patients had a positive effect on patient adherence. The researchers estimated that each incremental dollar in co-pay led to a 0.4% decrease in adherence so that a $10 co-pay increase equated to a 3.8% decline in adherence.[23]

As many low-cost generic formulations of statins are now available, high co-pays are more likely to affect use of newer, branded LLTs, such as PCSK9 inhibitors. In an analysis of the Family Heart Database™ in August 2015 to December 2017, 15% of patients prescribed a PCSK9 inhibitor did not pick up the medication from the pharmacy. The average co-pay for abandoned prescriptions was higher ($233.80) compared to the co-pay ($103.17) for retrieved prescriptions.[24]

HIGHER COPAYS
are associated with greater treatment abandonment[23]

ONLY
28%
OF PATIENTS
understood that taking an LLT would lower their risk for a heart attack or stroke[22]

PAYERS

Health insurance companies and pharmacy benefit managers use step therapy and prior authorization (PA) to limit uptake of new, higher-priced treatments. Step therapy requires patients try lower-cost, often less-effective treatments before the insurer will pay for the newer therapies. For patients with FH and/or ASCVD, step therapy prolongs their exposure to excessive LDL-C and risk for cardiovascular events.[25]

PA requirements, which differ by payer, typically involve data collection and completion of forms, some of which are lengthy (e.g., 17 pages).[25] The amount of physician office resources should not be discounted. The PA and appeals process for PCSK9 inhibitors can consume twice the resources compared to the PA/appeals for other branded, injectable therapies for the treatment of diabetes.[26]

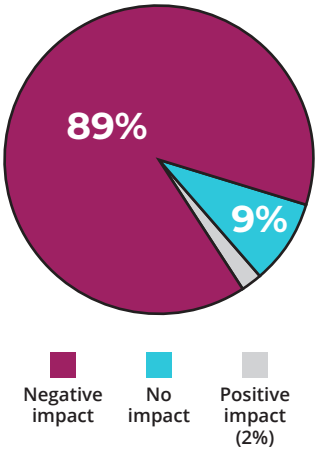
First requests for prescribed therapy are often rejected,[27] overwhelming busy clinicians with paperwork and appeals. While large health systems may have specialty pharmacists who assist with PAs, community health centers serving under- or uninsured patient populations are unlikely to have the benefit of specialty pharmacists, worsening health inequities for economically disadvantaged individuals.

The American Medical Association (AMA) conducted of a survey its members in 2022. Of the 1001 respondents, 89% indicated PA had a negative impact on patient clinical outcomes and 80% reported that PA could lead some patients to abandon treatment. In addition, PA has prompted use of less-effective treatments, according to 64% of physicians, and led to increases in office visits and emergency room visits. One-third of clinicians indicated that PA led to a serious adverse event for a patient in their care.[28]

A recent study by O'Neil et al analyzed the initial and durable rejection rates for PCSK9 inhibitors among >4.5M commercially insured patients during January 2018 to July 2021. The initial rejection rate for PCSK9 inhibitors was 91% and the durable rejection rate was 53%. The majority of rejections were related to the need for prior authorization and/or the payer requiring the patient undergo step therapy with other LLTs. Disconcertingly, most patients who received a rejection for a PCSK9 inhibitor (74%) did not receive another LLT, leading the researchers to conclude that new approaches were needed for drug pricing and access in the US.[27]

As demonstrated in previous research from the Family Heart Foundation, the impact of these rejections is not without consequences. An analysis of the Family Heart Database™ showed PCSK9i claim rejection rates for FH and ASCVD individuals of 58.5% and 58.3%, respectively, between August 2015 and December 2017. Overall, for patients whose PCSK9i claim was rejected versus paid, there was a 16% increase in the composite cardiovascular outcome despite a relatively short follow-up period of 341 to 411 days.[25]

PA NEGATIVE IMPACT ON CLINICAL OUTCOMES[28]



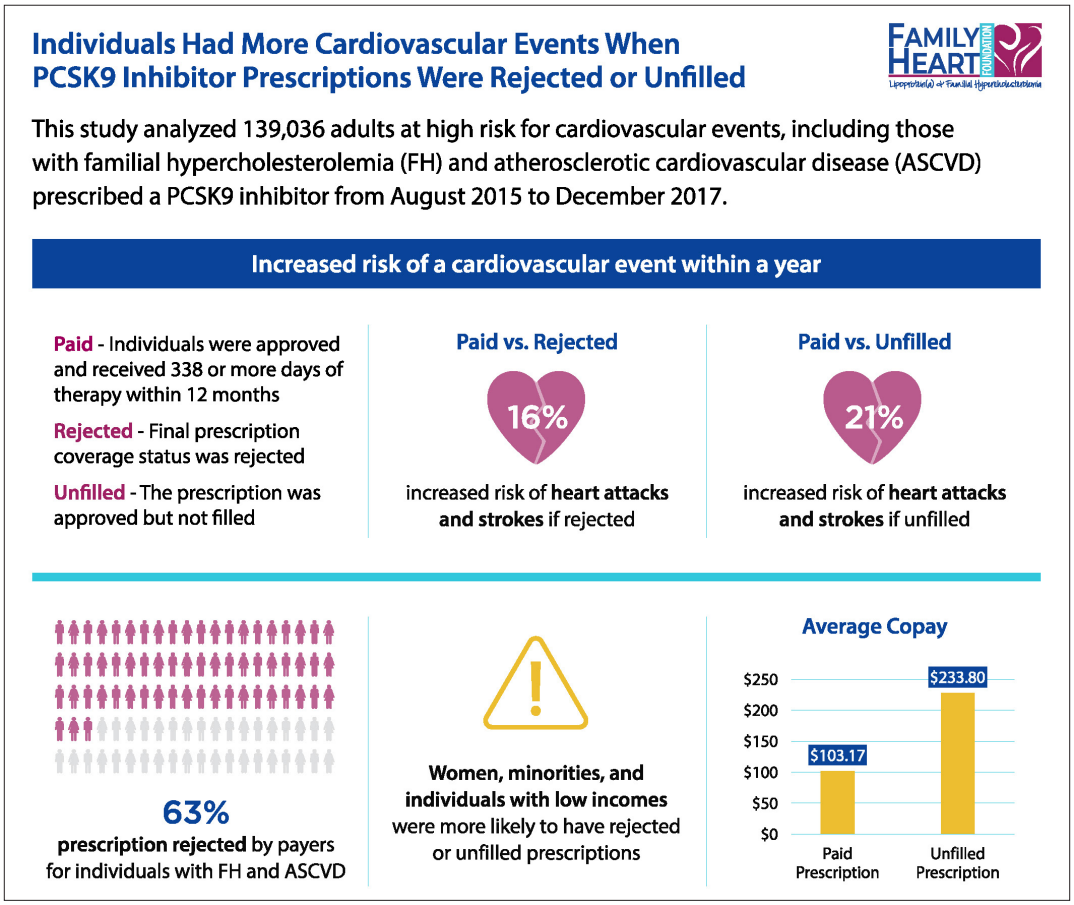
1/3
OF CLINICIANS
indicated that PA led to a serious adverse event for a patient in their care.

REJECTION RATES FOR PCSK9 INHIBITORS[27]

91%
initial rejection rate for PCSK9 inhibitors

74%
OF PATIENTS
received a rejection for a PCSK9 inhibitor and did not receive another LLT

PCSK9 INHIBITOR REJECTIONS OR ABANDONMENTS AND CV OUTCOMES



Source: Family Heart Foundation.

Pharmacy benefit managers (PBMs), which serve as the middle man between pharmaceutical companies and insurers, construct formularies of which drugs will be covered by a healthcare insurance plan and design rebate programs. PBMs have financial conflicts, which may be at the detriment of patients. For instance, a treatment's efficacy and safety alone may not be sufficient to place a medication on an approved formulary list. Other factors, such as cost and rebate agreements, can influence whether a treatment is covered by insurance.[29]

Pharmaceutical companies pay rebates to PBMs in order to secure a treatment's inclusion in a formulary. Not all of the rebate is passed onto the patient. Instead, the PBM takes a percentage of the rebate. Because of this, it is in the PBM's interest to have a higher list price of the medication. Combined with insurers' increasing shift to forcing patients into co-insurance arrangements (on top of copays), higher list prices can result in higher out-of-pocket costs for patients because the co-insurance percentage that a patient often pays is calculated off of the drug's list price, not the rebated net price that PBMs are paying.

Bills in the House of Representative and Senate have been introduced that would require greater transparency from PBMs with regard to negotiations with pharmaceutical companies, rebate information, drug prices, and design of formularies. Proposed legislation would also prohibit "spread pricing" in which the PBM reimburses a pharmacy at a lower rate than what it receives from health plan and captures the difference as profit, prevent PBMs from securing a percentage of rebates, and limit use of copay accumulator programs, which do not permit a patient's copays to be included in cost-sharing calculations.[30]

RECOMMENDATIONS FOR IMPROVING LDL-C CONTROL

WE ARE FAILING TO PREVENT UNNECESSARY SUFFERING AND DEATHS. THERE IS MISALIGNMENT OF INCENTIVES AMONG THOSE IN THE HEALTHCARE SYSTEM, AND THE AMERICAN PUBLIC IS PAYING THE HIGHEST PRICE FOR HOW THE BUSINESS OF HEALTHCARE IS RUN TODAY.

POLICY MAKERS

- **We recommend restoration of quality measures governing both LDL-C measurement as well as specific goals for high-risk patients, such as those with ASCVD and FH.** LDL-C quality measures were removed by the National Committee for Quality Assurance-Healthcare Effectiveness Data and Information Set (NCQA-HEDIS) in 2015. LDL-C measurement is a performance goal that is better aligned with value-based care delivery and may help overcome clinical inertia related to undertreatment of elevated LDL-C.
- **We support common-sense prior authorization reform.** Denial rates for nonstatin therapies are high, and these denials carry significant, negative consequences. We urged adoption of the common-sense principles endorsed by the American Medical Association (AMA), America's Health Insurance Plan (AHIP), and others.
- **We urge legislators to enact PBM reform to ensure greater transparency and to enable patients to fully benefit from drug rebate programs.**
- **We support legislation to limit the impact of co-pay accumulators** for patients who require branded lipid-lowering medications to manage their LDL-C.
- **We recommend significant investment by NHLBI, CDC, and other agencies in widespread public health messaging to raise the level of awareness, treatment, and control of LDL-C.** The National High Blood Pressure education program in the 1970s and the National Cholesterol Education program in the 1980s are excellent models.

PAYERS

- **We urge payers to reconsider current cost-sharing models that negatively affect patient adherence.** Statins (especially high-intensity statins such as atorvastatin 40 and 80mgs and rosuvastatin 20 and 40mgs) and ezetimibe should be made available on the lowest cost-sharing tier at health plans. Numerous studies have shown a clear and consistent relationship between patient out-of-pocket cost and medication adherence.
- **We recommended coverage of twice-yearly lipid panels with minimal patient cost sharing.**
- **We strongly support payer coverage of 90-day prescriptions,** which have been shown to have a positive impact on adherence for chronic medications.
- **We recommend simplification and streamlining of prior authorization.** The process for branded agents should be streamlined, including adoption of electronic prior authorization, standardized nonstatin forms across payers, and inclusion of "gold carding", i.e., prior authorization exemption for HCPs who had 90% of requests approved in the preceding 12 months.
- **We urge payers to be transparent with their formulary design and prior authorization criteria. Additionally, patient co-insurance costs should be calculated off of a drug's discounted net price, not the list price.**

HEALTHCARE PROVIDERS AND HEALTH SYSTEMS

- **HCPs should individualize therapy for patients, with upfront combination therapy for those with ASCVD, FH or at high-risk for developing cardiovascular disease who require more than a 50% reduction in LDL-C to achieve their target.**
- **HCPs should assess LDL-C 4 to 12 weeks after initiation of LLT and after any dosage adjustment and then repeat every 3 to 12 months as needed.**
- **We support and encourage a team-based approach to LDL-C management.** Team-based care using nurses, nurse practitioners, pharmacists, patient navigators, etc. has been shown to improve control of cardiovascular risk factors.
- **We urge health systems to leverage electronic medical record systems to enhance LDL-C control.** EMR system prompts ("nudges") for HCPs and text messaging to patients have shown improvements in initiation of guideline-based therapies for high-risk individuals.

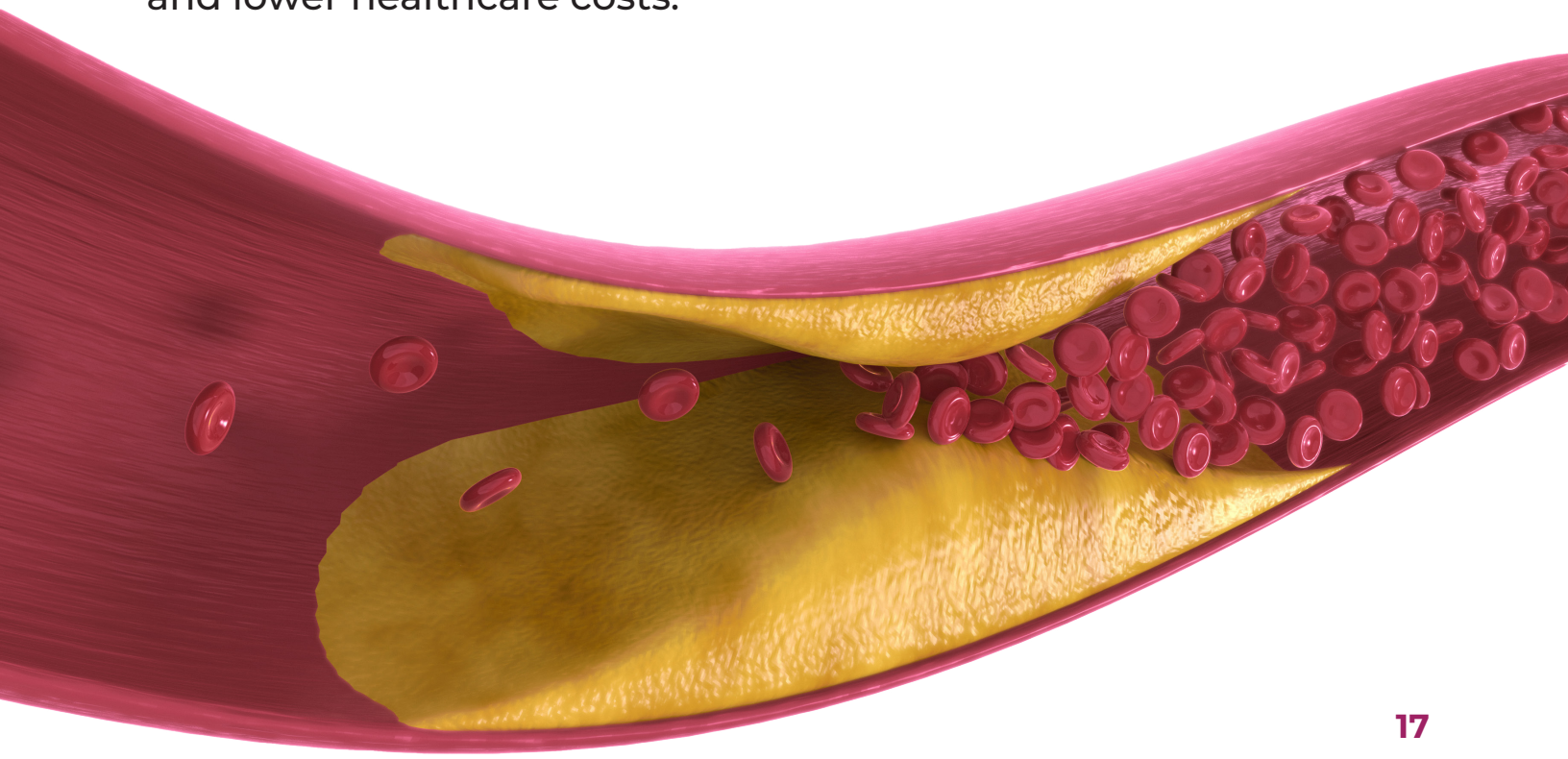
PATIENTS

- **We urge patients to educate themselves on cardiovascular disease, LDL-C goals, the importance of medication in LDL-C reduction, and why adherence to treatment plans benefits their health.**
- **We encourage patients to get their lipids assessed in the month prior to their HCP appointment** to facilitate shared decision making with the most current LDL-C values.
- **We counsel patients to know their rights in the event they are denied access to a medication or diagnostic test.** Resources provided by the Family Heart Foundation include:
  - The LDL Safe Zone website (www.ldlsafezone.org)
  - Navigating Insurance Brochure (https://familyheart.org/media/2020/06/Navigating-Insurance-Guide_20200327.pdf)

> **"CHOOSING MEASURES THAT ARE MOST CLOSELY ALIGNED WITH QUALITY OUTCOMES (E.G., LDL-C MEASUREMENT OR CONTROL VS. STATIN USE) IS FUNDAMENTAL TO VALUE-BASED CARE DELIVERY AND POPULATION HEALTH MANAGEMENT WITHIN HEALTH SYSTEMS."**
>
> **A Joint Clinical Perspective from the National Lipid Association and the American Society for Preventive Cardiology**

SUMMARY

Cardiovascular disease costs $403 billion annually, most of which stems from hospitalization costs. LDL-C is the most modifiable risk factor for cardiovascular disease, and LDL-C reduction has been proven to reduce the incidence of heart attack and stroke. Fewer than 30% of Americans at high risk for ASCVD or cardiovascular events have controlled LDL-C, placing them at substantially higher risk of cardiovascular events. Our analysis of the Family Heart Database™ found that patients with established ASCVD are spending too little time below the guideline-recommended goal of <70 mg/dl. Cardiovascular events were significantly higher in patients who had elevated LDL-C. All stakeholders—policymakers, physicians, health systems, patients, and payers—must take action to increase the percentage of patients who have controlled LDL-C to improve patient outcomes, reduce cardiovascular deaths, and lower healthcare costs.



ENDNOTES

1 Family Heart Foundation. Patient Provider Payor Lipid-Lowering Landscape (PPPLLL). 2023. Data on file.

2 Tsao CW, Aday AW, Almarzooq ZI et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. *Circulation*. 2023; 147: e93-e621.

3 Cholesterol Treatment Trialists' Collaboration (CTTC). Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170000 participants in 26 randomised trials. *Lancet*. 2010; 376: 1670-1681.

4 Lindh M, Banefelt J, Fox KM et al. Cardiovascular event rates in a high atherosclerotic cardiovascular disease risk population: estimates from Swedish population-based register data. *Eur Heart J Qual Care Clin Outcomes*. 2019; 5: 225-232.

5 Nair R, Johnson M, Kravitz K et al. Characteristics and Outcomes of Early Recurrent Myocardial Infarction After Acute Myocardial Infarction. *J Am Heart Assoc*. 2021; 10: e019270.

6 Plakht Y, Gilutz H, Shiyovich A. When More Means Less: The Prognosis of Recurrent Acute Myocardial Infarctions. *J Clin Med*. 2021; 10: 5889.

7 Grundy SM, Stone NJ, Bailey AL et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019; 139: e1082-e1143.

8 Lloyd-Jones DM, Morris PB, Ballantyne CM et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2022; 80: 1366-1418.

9 Cannon CP, de Lemos JA, Rosenson RS et al. Use of Lipid-Lowering Therapies Over 2 Years in GOULD, a Registry of Patients With Atherosclerotic Cardiovascular Disease in the US. *JAMA Cardiol*. 2021; 6: 1-9.

10 Aggarwal R, Chiu R, Libby P et al. Low-Density Lipoprotein Cholesterol Levels in Adults With Coronary Artery Disease in the US, January 2015 to March 2020. *JAMA.* 2023; 330: 80-81.

11 Gao Y, Shah LM, Ding J, Martin SS. US Trends in Cholesterol Screening, Lipid Levels, and Lipid-Lowering Medication Use in US Adults, 1999 to 2018. *J Am Heart Assoc*. 2023; 12: e028205.

12 Klimchak AC, Patel MY, Iorga ŞR et al. Lipid treatment and goal attainment characteristics among persons with atherosclerotic cardiovascular disease in the United States. *Am J Prev Cardiol*. 2020; 1: 100010.

13 Nelson AJ, Haynes K, Shambhu S et al. High-Intensity Statin Use Among Patients With Atherosclerosis in the U.S. *J Am Coll Cardiol*. 2022; 79: 1802-1813.

14 Bradley CK, Kolkailah AA, Shah NP et al. Uptake of non-statin lipid-lowering therapies for secondary prevention in community practice. *J Clin Lipidol*. 2023; 17: 412-414.

15 Banach M, Penson PE, Vrablik M et al. Optimal use of lipid-lowering therapy after acute coronary syndromes: A Position Paper endorsed by the International Lipid Expert Panel (ILEP). *Pharmacol Res*. 2021; 166: 105499.

16 Lewek J, Niedziela J, Desperak P et al. Intensive statin therapy versus upfront combination therapy of statin and ezetimibe in acute coronary syndrome patients. A propensity score matching analysis based on the PL-ACS Registry data. *Lancet*. 2023; PREPRINT: http://dx.doi.org/10.2139/ssrn.4357916.

17 Lee SJ, Cha JJ, Choi WG et al. Moderate-Intensity Statin With Ezetimibe Combination Therapy vs High-Intensity Statin Monotherapy in Patients at Very High Risk of Atherosclerotic Cardiovascular Disease: A Post Hoc Analysis From the RACING Randomized Clinical Trial. *JAMA Cardiol*. 2023;

18 Koskinas KC, Catapano AL, Baigent C et al. Current perceptions and practices in lipid management: results of a European Society of Cardiology/European Atherosclerosis Society Survey. *Eur J Prev Cardiol*. 2022; 28: 2030-2037.

19 Zullig LL, Egbuonu-Davis L, Trasy A et al. Countering clinical inertia in lipid management: Expert workshop summary. *Am Heart J*. 2018; 206: 24-29.

20 Adusumalli S, Kanter GP, Small DS et al. Effect of Nudges to Clinicians, Patients, or Both to Increase Statin Prescribing: A Cluster Randomized Clinical Trial. JAMA Cardiol. 2023; 8: 23-30.

21 Colantonio LD, Rosenson RS, Deng L et al. Adherence to Statin Therapy Among US Adults Between 2007 and 2014. J Am Heart Assoc. 2019; 8: e010376.

22 Arnold SV, Cannon CP, de Lemos JA et al. What Do US Physicians and Patients Think About Lipid-Lowering Therapy and Goals of Treatment? Results From the GOULD Registry. J Am Heart Assoc. 2021; 10: e020893.

23 Eaddy MT, Cook CL, O'Day K et al. How patient cost-sharing trends affect adherence and outcomes: a literature review. P T. 2012; 37: 45-55.

24 Myers KD, Farboodi N, Mwamburi M et al. Effect of Access to Prescribed PCSK9 Inhibitors on Cardiovascular Outcomes. Circ Cardiovasc Qual Outcomes. 2019; 12: e005404.

25 Baum SJ, Toth PP, Underberg JA et al. PCSK9 inhibitor access barriers-issues and recommendations: Improving the access process for patients, clinicians and payers. Clin Cardiol. 2017; 40: 243-254.

26 Warden BA, Purnell JQ, Duell PB et al. Real-world utilization of pharmacotherapy with new evidence-based cardiovascular indications in an academic preventive cardiology practice. *Am J Prev Cardiol*. 2021; 5: 100144.

27 O'Neil A, Calderbank S, Brown J et al. Quantification of Utilization Management Barriers for Patients Initiating Therapy to Lower Lipid Levels. *JAMA Netw Open*. 2022; 5: e2240513.

28 American Medical Association (AMA). 2022 AMA prior authorization (PA) physician survey. 2023; Accessed at: https://www.ama-assn.org/system/files/prior.

29 Feldman MA. Pharmacy benefit managers' impact on patient access. Alliance for Patient Access. July 2023. Accessed at: https://allianceforpatientaccess.org/wp-content/uploads/2023/07/AfPA_Pharmacy-Benefit-Managers-Impact-on-Patient-Access_Physicians-Perspective_July-2023.pdf

30 Slifer E, Llamas A. Bipartisan Congressional support for PBM reform grows. The Commonwealth Fund. Blog, June 21, 2023. Accessed at: https://www.commonwealthfund.org/blog/2023/bipartisan-congressional-support-pbm-reform-grows

31 Stone NJ, Robinson JG, Lichtenstein AH et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014; 129: S1-45

32 Virani SS, Aspry K, Dixon DL et al. The importance of low-density lipoprotein cholesterol measurement and control as performance measures: A joint clinical perspective from the National Lipid Association and the American Society for Preventive Cardiology. *Am J Prev Cardiol*. 2023; 13: 100472.

33 Cannon CP, de Lemos JA, Rosenson RA, Ballantyne CM. What Do US Physicians Think About Lipid-Lowering Therapy and the Guidelines? Results From a National Survey in the Getting to an ImprOved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia Management (GOULD) Registry. American Heart Association annual meeting. Nov 10-12, 2018; Chicago, IL.

PRIORITIZING LDL-CHOLESTEROL CONTROL

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