AmerisourceBergen
Xcenda

July 2021

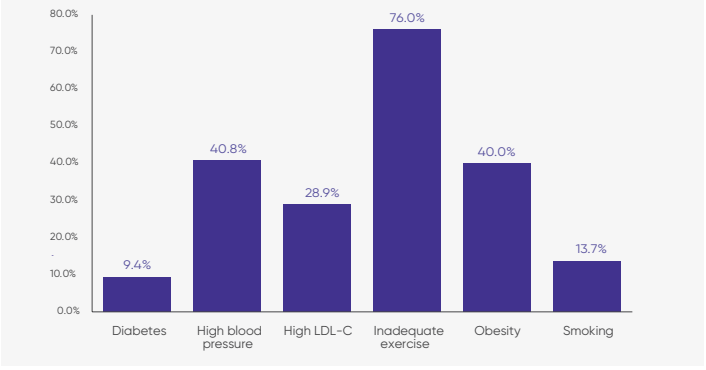
Executive Summary

Undervaluing diagnosis and treatment of ASCVD

Atherosclerotic cardiovascular disease (ASCVD) is insidiously common—it is the leading cause of death in the United States and the underlying cause in about 50% of all deaths in Western societies. It is known more commonly by its myriad of negative outcomes, including myocardial infarction (MI), angina, stroke/transient ischemic attack, peripheral artery disease, heart failure, and atrial fibrillation, than by the collective term ASCVD.

Diagnosis of ASCVD often occurs later in life, commonly after a negative clinical event such as an MI or stroke, but the groundwork for it is laid years or decades prior. Diabetes and high blood pressure (HBP) are on the rise, while controlled HBP has decreased, and these negative outcomes are increasing in adolescence and young adulthood among US patients; these diseases are also part of the foundation of ASCVD clinical events later in life. Thus, a best-case scenario would start prevention of clinical ASCVD early in life.

Figure 1. Percentage of adult US population with ASCVD risk factors



Beyond healthier diets, smoking cessation, and other cardiovascular disease (CVD) prevention methods, treatment options exist that target the main risk factors for ASCVD development, primarily HBP, high low-density lipoprotein cholesterol (LDL-C), and diabetes. But control of these diseases remains poor in the US (while prevalence continues to increase), and access challenges, clinical inertia, and poor adherence are barriers to effective prevention and treatment. And the devastating outcomes of ASCVD require change: ~60% of deaths due to ASCVD occur in people aged ≤65 years old, over 1,000 deaths per day are caused by ASCVD-related events, and the age-adjusted death rate for it is 219.4 per 100,000 people in 2017.

Then there is the crushing economic impact associated with the disease: 2015 national expenditures were estimated at $126 billion and projected to rise to $309 billion by 2035; a 2016 study estimated total (direct and indirect) costs of ASCVD at a staggering $555 billion, a number that is expected to grow to over $1.1 trillion by 2035, when 45% of the US population is estimated to have some form of ASCVD. Thus, a clear and significant need exists for more, and better, therapies to slow the clinical, economic, and human damage caused by ASCVD.

Unfortunately, there is no magic bullet to improve outcomes. Many of the first-line prescription drugs to lower risk factors for ASCVD are low-cost generics and thus have broad coverage among payers. Despite the easy access to high-value drugs, there are persistent gaps in adherence. A 2019 study from the Intermountain Healthcare Heart Institute in Salt Lake City determined that only about 6% of CVD patients followed their physicians' instructions on taking statins, while adherence with hypertension medication 1 year after initiation is typically reported at less than 50%.

Medication nonadherence is multifactorial; several studies have demonstrated the association between nonadherence and patients' beliefs, socioeconomic status, health literacy, and race/ethnicity. This lack of adherence is associated with the various adverse outcomes discussed in this paper, such as increased costs, poorer quality of life, and death. Other patients with adverse outcomes simply do not respond—or respond well—to the available therapies, despite fully complying with their physicians' instructions. This biologic basis for a less-than-average response shows the need and opportunity for continued innovation to develop treatments for the spectrum of people with ASCVD.

Improving outcomes will require a multifactorial approach, with players in all parts of the healthcare system working to identify risk factors, minimize or reverse the increasing prevalence of certain diseases, and effectively treat these diseases with all the tools available to us. Like other chronic conditions, this will require a team-based medical approach with shared decision making.

Earlier and more testing is needed: The 2018 American Heart Association Guideline for the Management of Blood Cholesterol recommends earlier screening and earlier treatment. Screening for hypercholesterolemia is recommended for children as young as 9 years old, even in the absence of a strong family history of CVD. The guideline also recommends that adults aged 20 years and older should have lipid panels every 4 to 6 years, beginning at age 21. The sooner patients at risk of ASCVD can be identified, the sooner remediation measures can be implemented.

Access to lipid-lowering therapies needs to increase: Guidelines stress the importance of rapid attainment of targets to maximize preventive benefits of LDL-C-lowering therapies; in other words, the goal for patients should be to reduce LDL-C levels "as much as possible as fast as possible." This can be achieved, in part, with the use of adjunct nonstatin medications and lowering associated out-of-pocket costs.

Access to prescription drugs to facilitate prevention should be streamlined: Provider offices often struggle under the complex and burdensome prior authorization, approval, and appeals processes for patients, with a 2017 study finding that offices can spend 4 to 6 hours *per patient* in order to get a drug approved for coverage. The delays that come from filing paperwork and corresponding with payers and patients result in treatment delays that can have adverse outcomes for patients: A 2018 American Medical Association survey found that more than 9 in 10 physicians (92%) said the prior authorization process delays patient access to necessary care, and nearly 4 in 5 physicians (78%) report that prior authorization can sometimes, often, or always lead to patients abandoning a recommended course of treatment. To address this, attention is on developing standardized prior authorization forms that are universally applicable, reflect recommendations from the current guidelines, and also ensure that clinicians are held accountable for appropriate prescription patterns.

Pharmaceutical and medical innovation is needed: Providing additional choice and competition in the market conveys benefits in terms of clinical appropriateness, cost, and patient preferences. Perhaps the next advance could be regimens with longer half-lives, patches that offer controlled-release formulations, or other inventions that have not yet been imagined.

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Undervaluing diagnosis and treatment of ASCVD

Introduction

Sometimes there is something so common that it hides in plain sight. An example is atherosclerotic cardiovascular disease (ASCVD), a condition that is highly prevalent and yet under-recognized. Over 20 million United States (US) adults have this type of heart disease, and it is the leading cause of death in the US and the underlying cause of about 50% of all deaths in Western societies.[1-3] Most people know it by its outcomes—myocardial infarction (MI) or heart attack, stable or unstable angina, stroke/transient ischemic attack, peripheral arterial disease, heart failure, and atrial fibrillation—rather than by the condition itself.[4]

Atherosclerosis is a general term that refers to a disease of the arteries that results from exposure of the arterial wall to risk factors such as elevated cholesterol and high blood pressure (HBP).[5] This damages the arterial wall and leads to the formation of plaque. If the plaque loosens and breaks away from the wall, it may cause clinical ASCVD, which can manifest itself as a stroke, a heart attack, or damage to peripheral arteries in the legs—all of which can lead to death.

There are several treatments currently approved with the indication of preventing or treating ASCVD by targeting various risk factors of ASCVD, such as HBP, high low-density lipoprotein cholesterol (LDL-C) (aka, "bad cholesterol"), and diabetes. However, many patients remain under- or untreated—in part due to access challenges, clinical inertia, and poor adherence to therapies. According to the Centers for Disease Control and Prevention (CDC)[6]:

- Almost half of the US adults (45%, or 35 million) who could benefit from cholesterol-lowering medicines are not currently taking them.[7]
- Even among patients with established ASCVD who are at very high risk, approximately 80% have elevated LDL-C.[8]
- Nearly half of adults in the US (108 million, or 45%) have hypertension.[9]
- Most adults with hypertension in the US (82 million) do not have their hypertension under control.[9]

Additionally, the science of cholesterol and lipoproteins is developing rapidly; as a result, patients run the risk of being misdiagnosed, potentially delaying proper treatment for their conditions.

ASCVD also has a crushing economic impact on our society. National expenditures for ASCVD were $126 billion in 2015 and are projected to increase by over 2.5-fold to $309 billion in 2035.[10] In total, after accounting for indirect costs of lost productivity, these costs are expected to increase from $322 billion to $509 billion over this period.

There is room (and need) for more—and better—approaches for ASCVD. However, outdated policies and general payer reluctance are barriers to improving ASCVD management, exacerbating the burden on patients, the US health system, and the economy. In addition to payer-imposed access barriers, misaligned incentives have limited innovation in ASCVD prevention. This white paper demonstrates how widespread ASCVD is and the treatment gaps leading to its prevalence.

Current screening and ASCVD prevention in the US

ASCVD diagnosis occurs too late

What can be frustrating is that ASCVD is often diagnosed when it is too late (eg, after an MI or stroke), while addressing risk factors earlier could have prevented those consequences.

> A best-case scenario would start prevention of ASCVD early in life.

An umbrella of different conditions—such as acute coronary syndromes, a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease—are presumed to be of atherosclerotic origin.[11]

Early prevention is the best medicine

Much of atherosclerosis begins years before overt disease, in adolescence and young adulthood.[4] The prevalence of certain predisposing factors has increased, including obesity[12] and diabetes,[13] and the prevalence of controlled blood pressure has declined.[14] These unfavorable trends have also been observed among youths and younger adults. As a result of these factors and trends, health experts expect the population with CVD (comprising coronary heart disease, heart failure, stroke, and hypertension) to expand dramatically in years to come. Progression of atherosclerosis manifests clinically as ASCVD in middle age or later years. Thus, a best-case scenario would start prevention of clinical ASCVD early in life.

One approach to drive down clinical ASCVD is quitting smoking. Cigarette smoking, the most common form of tobacco use, is a major risk factor for CVD and stroke.[15] The good news is that current smoking has declined from 20.9% in 2005 to 14.0% in 2019, and the proportion of smokers who have quit has increased.[16] The antismoking campaign is a major success with few parallels in the history of public health.[17]

Beyond healthier diets, smoking cessation, and other CVD prevention methods, there are 3 modifiable risk factors that predict CVD events: HBP, high LDL-C, and diabetes.[18] The 2019 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Primary Prevention of Cardiovascular Disease outlines treatments for those 3 conditions for the primary prevention of CVD, as described below.[4]

High blood pressure

HBP (aka, hypertension) is a symptomless "silent killer" that quietly damages blood vessels and leads to serious health problems, including ASCVD.[19] Physicians will usually recommend that patients with HBP adopt a "heart-healthy lifestyle" that includes choosing healthy foods, avoiding or limiting alcohol, getting regular exercise, aiming for a healthy weight, quitting smoking, managing stress, and getting sufficient quality sleep.[20]

> Every 10 mmHg increase in systolic blood pressure increases the risks of coronary heart disease, stroke, or other ASCVD events by 53%

When healthy lifestyle changes alone do not control or lower HBP, the patient's physician may prescribe blood pressure medicines, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers, diuretics, or beta blockers. A 2020 study used data from 1,457 participants without ASCVD who were followed for a mean of 14.5 years to examine the relationship between systolic blood pressure and ASCVD in patients without ASCVD risk factors or hypertension.[21] As the systolic blood pressure level increased, ASCVD risk factors, incident ASCVD events, and coronary artery calcium increased. In fact, for every 10 mmHg increase in systolic blood pressure, the risks of coronary heart disease, stroke, or other ASCVD events jumped 53%—hence the overhanging danger posed to the millions of individuals with uncontrolled HBP.

High cholesterol

Dozens of studies in hundreds of thousands of patients over the past few decades have shown that lowering LDL-C reduces the risk of a first or recurrent ASCVD event (such as a heart attack). As such, the most recent guidelines to reduce the risk of ASCVD through cholesterol management emphasizse that LDL-C should be lowered with lifestyle and therapies depending on an individual's ASCVD risk.[22] Medicines that are recommended by the guidelines to lower LDL-C include statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

Some genetic causes of high cholesterol mean certain people are essentially guaranteed to have life-threatening ASCVD and be placed on maximally tolerated therapy before symptoms arise. We detail a couple of such conditions below.

Dyslipidemias are greatly undertested and underdiagnosed

Many people have unusually high LDL-C levels that contribute to the development of atherosclerosis. Dyslipidemia is elevation of plasma cholesterol, triglycerides, or both, or a low high-density lipoprotein-C (HDL-C) level that contributes to the development of atherosclerosis.[23]

Diagnosis is made by measuring plasma levels of LDL-C and other lipids. However, because its early stages present no symptoms, dyslipidemia often remains undiagnosed until patients begin presenting with vascular complications.[24]

Many patients with high LDL-C have a combination of genetic predisposition and exacerbating factors such as lifestyle, age, and diet. The guidelines recommend that all patients with established ASCVD should receive cholesterol-lowering medicines, because lifestyle changes alone are rarely enough. However, even among the highest-risk patients—those with established ASCVD—many remain undertreated.[8]

Familial hyperlipidemia (FH) is a genetic disorder that produces extreme elevations in LDL-C; most patients with FH do not know they have it.[25] High levels of circulating LDL-C lead to the rapid development of atherosclerosis early in life, which results in the premature development of ASCVD. Additionally, approximately 1 in 3 individuals with FH also have a lipoprotein(a) (Lp[a]) level high enough to be a significant accelerant of ASCVD.[26] (Lp[a] is discussed in the next section.) The literature shows that early diagnosis and initiation of lipid-lowering treatment are associated with a significant reduction in the risk of developing ASCVD.[27]

A DNA diagnosis remains the gold standard to diagnose FH.[28] However, genetic testing is underutilized in many parts of the world.[29] Data from the Cascade Screening for Awareness and Detection of FH Registry in the US showed that genetic testing had only been performed in 3.9% of individuals with a clinical diagnosis of FH.[30]

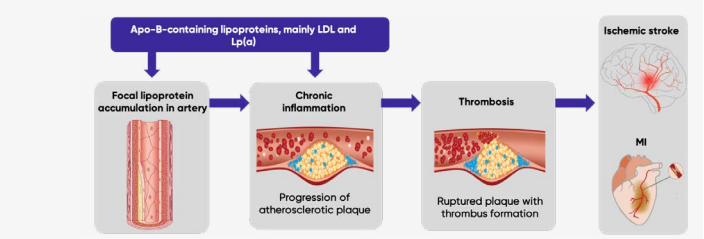
Lp(a) confers high ASCVD risk

Lipoproteins are a mesh of proteins and fats that help carry cholesterol in the blood. Lp(a) is an LDL-like substance containing a protein called apolipoprotein(a). Lp(a) is made in the liver and carries fats and other lipids such as cholesterol around the body.[31]

Lp(a) levels are largely determined by genetics and remain more or less stable throughout a person's life.[26] Elevated Lp(a) levels are another type of dyslipidemia.

Studies focusing on genetic variation and risk of disease found that high Lp(a) concentrations confer the highest risk of ASCVD, independent of other known causes and risk factors.[32] And, adding cause for concern, statins tend to increase Lp(a) levels by 10% to 20%.[33]

Figure 2. Elevated LDL and Lp(a) levels are dominant risk factors for ASCVD



Key: Apo-B – apolipoprotein B; LDL – low-density lipoprotein; Lp(a) – lipoprotein(a); MI – myocardial infarction.

There are currently no approved therapies to treat elevated Lp(a).[33] Physicians trying to treat elevated Lp(a) are limited to using therapies with limited efficacy and sometimes severe side effects.

Recent consensus statements suggest that patients should be tested for Lp(a) levels.[26,34] The statements recommend treating patients with elevated Lp(a) with aggressive LDL-C reduction to lower the risk conferred by modifiable risk factors.

Despite the documented evidence for the role of Lp(a) in several CVDs across ethnicities and the high burden of Lp(a)-associated disease, there remains tremendous clinical inertia for measurement of Lp(a) in North America and worldwide.[35] An estimated 1.4 billion people globally (20%) have elevated Lp(a) sufficient to place them at high risk of developing ASCVD.[36] Of the approximately 60 million Americans with high Lp(a), the majority have not yet been identified. Dr. George Thanassoulis, the Director of Preventive and Genomic Cardiology at McGill University Health Center, stated in a commentary, "Indeed, a compelling argument can be made that all individuals should have Lp(a) measured at least once in their lifetime, given that levels remain largely stable throughout life." This stability holds regardless of whether the person's Lp(a) levels are in the low, normal, or high range.

> *"Indeed, a compelling argument can be made that all individuals should have Lp(a) measured at least once in their lifetime, given that levels remain largely stable throughout life."*
>
> – Dr. George Thanassoulis, the Director of Preventive and Genomic Cardiology at McGill University Health Center

Diabetes

The most recent studies have shown that an aggressive, comprehensive approach to ASCVD risk factor management in adults with diabetes reduces ASCVD events.[30]

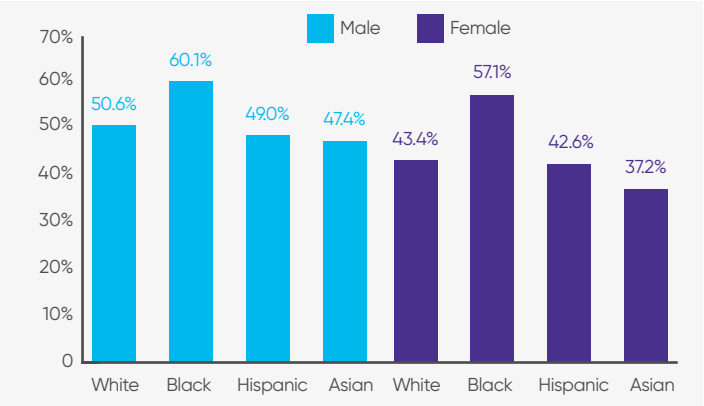
The development and progression of type 2 diabetes are heavily influenced by dietary patterns, physical activity, and body weight. Approximately 12% of US adults have diabetes, 90% to 95% of whom have type 2 diabetes, with significant heterogeneity according to age, sex, race/ethnicity, and socioeconomic status. The development and progression of type 2 diabetes are heavily influenced by dietary patterns, physical activity, and body weight. Alarmingly, more than one-third of US adults (≈80 million adults) have prediabetes and are at risk of developing type 2 diabetes, pointing to the urgency to prevent diabetes development.

ASCVD risk factors and treatment exacerbate health disparities

While there are limited data on ASCVD stratified by race or ethnicity, racial and ethnic minorities in the general population have a higher prevalence of ASCVD compared with non-Hispanic White individuals.[37]

According to the most recent data, CVD affects a greater percentage of Black and White adults compared to Hispanic and Asian adults, aged ≥20 years, as shown in **Figure 3.**

Figure 3. Total CVDe prevalence,[a] 2013–2016: Aged ≥20 years

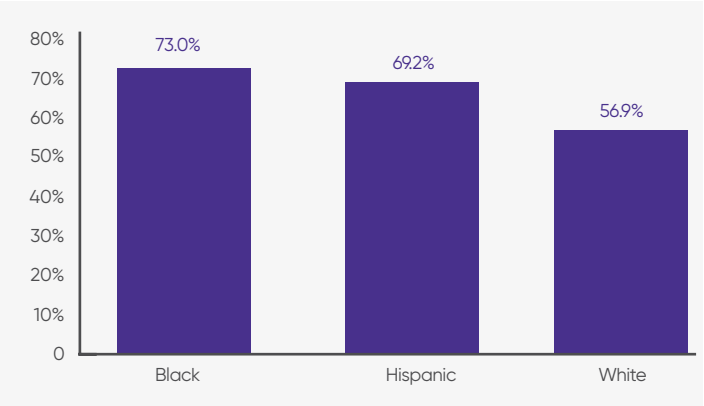


[a] Total CVD prevalence includes coronary heart disease, heart failure, stroke, and hypertension.
Key: CVD – cardiovascular disease.

In addition, researchers have documented minority groups as having higher rates of cardiovascular risk factors and worse outcomes compared with non-Hispanic White patients.[38] As a result, CVD mortality is higher in Black adults compared with Hispanic and White adults, which is explained partly by a higher prevalence of certain risk factors, delayed treatment, and decreased awareness and/or access to primary prevention measures.[18]

Some minority groups also have decreased access to effective medications, which results in poorer health.[36] For example, statins are effective in the primary and secondary prevention of ASCVD but are underutilized, especially in Black and Hispanic adults younger than 65 years. One study reviewed how Black, Hispanic, and White individuals at risk of having an ASCVD event would benefit from statin therapy but were not on it. The researchers found that Black and Hispanic individuals younger than 65 would benefit more—via fewer ASCVD events—than White individuals using statin therapy, as shown in Figure 4.

Figure 4. Proportional reduction of ASCVD events with statin therapy



Key: ASCVD – atherosclerotic cardiovascular disease.

Even as overall mortality rates for patients with ASCVD have declined over the last few decades across racial and ethnic groups, the decline has been less in Black adults compared to non-Hispanic White adults.[39] More studies are needed to precisely determine what causes the disparities and different degrees of ASCVD among ethnicities.

The costs of ASCVD are crippling

ASCVD has a high mortality rate

Since atherosclerosis is a predominantly asymptomatic condition, with patients often not knowing they have it until they have a negative outcome, it is difficult to determine the incidence accurately. Atherosclerosis is considered the major cause of CVDs, mainly involving the heart, brain, and arteries; namely, ischemic heart disease, ischemic stroke, and peripheral artery disease. Ischemic heart disease and stroke are the world's first- and second-leading causes of death, respectively.[40]

ASCVD is a lethal condition and kills many people before they have a chance to reach late middle age—approximately 60% of deaths due to ASCVD occur in patients aged ≤65 years.[41] In 2016, there were approximately 2.2 million total hospitalizations and over 1,000 deaths per day caused by ASCVD-related events, and 33% of life-changing cardiovascular events occurred in adults aged 35 to 64 years.[8] The age-adjusted death rate attributable to ASCVD was 219.4 per 100,000 in 2017.[8]

Enormous economic burden across the US and downstream patient impact

ASCVD burdens society with enormous costs. According to a 2016 study, the estimated total (direct and indirect) costs of ASCVD were $555 billion.[10] **Further, the study estimated that 45% of the US population will have some form of ASCVD by 2035, with associated total costs potentially reaching $1.1 trillion.**[10] This rapid increase in ASCVD-related costs has significant consequences for payers, providers, and patients.

At the patient level, ASCVD patients incur substantial medical care costs driven by ASCVD-related hospitalizations.[42] One investigation of the costs incurred by patients with ASCVD found that healthcare costs were extensive and exceeded $20,000 annually for patients with ASCVD, with average annual out-of-pocket (OOP) spending exceeding $2,000.[43]

45% of the US population will have some form of ASCVD by 2035, with associated total costs potentially reaching $1.1 trillion.

Overall, for families with a member with ASCVD, nearly 16% of the household income is spent on OOP healthcare expenditures.

Families of 3.9 million nonelderly adults (aged <65 years) with ASCVD and 45% of families with a member with ASCVD reported significant difficulty paying medical bills over a 12-month period.[44]

1 in 5 adults with ASCVD, representing 1.6 million nonelderly adults, was **unable to pay any medical bills.**

1 in 8 patients with ASCVD report nonadherence to medications because of cost, representing nearly 1.5 million estimated patients missing doses, 1.6 million taking lower-than-prescribed doses, and 1.9 million intentionally delaying a medication fill to save costs.

Dramatically reduced quality of life (QoL)

QoL can be affected adversely by an ASCVD diagnosis. Depression is a risk factor for the development of coronary heart disease in healthy patients and for adverse cardiovascular outcomes in patients with established heart disease.[45] Depression is present in 1 of 5 outpatients with coronary heart disease and in 1 of 3 outpatients with congestive heart failure.

ASCVD's impact on QoL is different for women than men. Women with ASCVD have been found to report lower health-related QoL, with a poorer perception of their health compared to men.[46]

Lost productivity

ASCVD is also costly, both in terms of loss of productivity and expected lifetime earnings for individuals who have the disease.

Current estimates of lost productivity involving days spent in bed, need for additional care, and lost earnings are estimated at $237 billion and are expected to grow to $368 billion by 2035.[10] The loss in productivity likely increases costs for the Social Security Disability Insurance and employer disability/health plans. ASCVD affects patients but can also increase costs enormously for businesses and the government.

ASCVD is costly, both in terms of loss of productivity and loss of expected lifetime earnings for individuals who have the disease.

ASCVD treatments face policy and reimbursement challenges

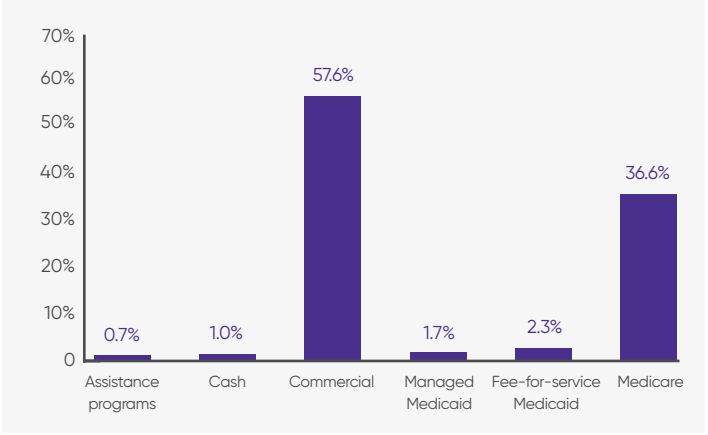
Many of the first-line prescription drugs to lower risk factors for ASCVD are low-cost generics, so payers typically allow broad access. However, some of the newer—and highly effective—drugs to treat conditions that can lead to ASCVD (eg, diabetes, HBP, and high cholesterol) are not available generically, and payers manage access through high OOP costs and utilization management (UM) tools such as prior authorization and step therapy. These tools create barriers that delay or prevent access to patients who can benefit from the medications that lower risk factors due to the additional steps and hassles needed to comply with UM requirements. As a result, fewer people can control their ASCVD progression, which leads to the various adverse outcomes discussed in this paper, such as increased costs, poorer QoL, and death.

Payer mix assessment

Xcenda conducted a payer mix analysis to quantify the likely distribution of the ASCVD patient population by primary payer types. The payer mix estimates the types of public and private payers reimbursing providers for ASCVD services, including for the uninsured (date range: November 2018–November 2020).

The payer mix results show that patients will most likely have commercial coverage (~58%), followed by Medicare (~37%) and Medicaid (~4%).[47] About 1% of patients will pay cash, and <1% of patients may require non-governmental assistance programs to cover the costs of care and medication, such as private foundations or hospital charity funds.

Figure 5. Likely distribution of ASCVD patient population by primary payer types



Key: ASCVD – atherosclerotic cardiovascular disease.

Accordingly, this section will address hurdles facing some patients to have prescription drugs covered that can lower their risk profile for ASCVD.

Patients face barriers obtaining ASCVD treatments

Not enough patients can access powerful LDL-C-reducing medications

Despite the powerful LDL-C-reducing capabilities of statins, ezetimibe, and PCSK9 inhibitors, not enough of the patients who could benefit from these treatments can access them.

Statins are typically the first-line treatment for patients with elevated LDL-C. Beyond efficacy and safety, they are also an ideal choice for many patients because they are available as inexpensive generics with many variants, allowing physicians to select the best statin for their patients.

While statins have had a positive effect on cardiovascular outcomes in the last decades, the large majority of patients with ASCVD have elevated LDL-C despite being on a statin.[8]

Studies show that many qualified patients with high LDL-C are not receiving appropriate lipid-lowering medication.

This is a combination of factors: people may have side effects at higher doses of statins, statins may not be powerful enough, or patients may struggle to be fully adherent to daily pills. The prevalence of poor adherence and the effect on mortality have been clearly shown.[48]

Team-based, coordinated care can help drive adherence so the patients get maximum benefit from the therapy. Nevertheless, for some patients, statin therapy is insufficient to drive down LDL-C or lipoprotein concentrations to healthy levels. Those populations need access to other medications, such as ezetimibe or PCSK9 inhibitors. Even those medications may not be sufficient or appropriate due to genetic factors. In those situations, further innovation is desperately needed.

Medicare Part D specialty tier drugs
The specialty tier is the highest category a health plan uses in organizing prescription drug coverage. The tier is often reserved for highly specialized drugs serving a small patient population, and it usually requires a significant OOP payment from patients. Coinsurance on specialty tier medications can be up to 33% of a drug's price, which is more than many seniors on fixed, modest incomes can pay.[49]

High OOP costs can discourage use

Another potential barrier facing patients is OOP costs for their drugs to treat underlying risk factors, such as diabetes or high LDL-C. For example, the 2 PCSK9 inhibitors launched at an annual list price of more than $14,000; payers responded by clamping down on patient access.[50,51] By 2018, however, facing competition and needing to increase sales, manufacturers of both PCSK9 inhibitors slashed the annual list prices of their drugs to between $4,500 and $8,000.[45,52]

As a result of the price cut, beginning in 2020, PCSK9 inhibitors no longer qualified as Medicare Part D specialty tier drugs ($670 per month in 2020), according to former Centers for Medicare & Medicaid Services (CMS) administrator Seema Verma.[53] As a result, patients should have paid less OOP for PCSK9 inhibitors, enabling the medications to be more accessible for those at risk for heart attack, stroke, or cardiovascular-related death.[54] However, despite the prospect of having access to much more affordable PCSK9 inhibitors, a study of 2020 Part D formularies determined that while all plans removed PCSK9 inhibitors from the specialty tier, only a third of all Medicare Part D beneficiaries could access those products on preferred brand tiers in 2020.[55] Instead, most Part D plans shifted PCSK9 inhibitors to nonpreferred tiers, which can be associated with even higher OOP costs than the specialty tier.

The cost-share difference of the preferred brand tier compared to the nonpreferred brand tier and the specialty tier is vast, as shown in **Table 1.**

Table 1. Median cost-sharing amounts for Medicare Part D plans in 2020[56]

	Preferred brand tier	Nonpreferred brand tier	Specialty tier
Median cost-share for Medicare Part D plans	$42	38%	25%
Monthly cost-share for a fictitious $1,000/month drug	$42	$380	$250

CMS caps coinsurance for Part D plan specialty tiers between 25% and 33%; however, cost-sharing for nonpreferred drug tiers can be as high as 50%, making the cost-share difference in Table 1 even more stark.[56] The formulary analysis found that, in 2020, the majority of patients without low-income subsidies under Part D will continue to face high monthly costs.[57]

Despite the plethora of available antihypertensive medications, blood pressure remains uncontrolled

While it is easy to point at PCSK9 inhibitors and say that they are an exception because of their prices, the treatments for HBP show that access concerns are broader. A range of available treatments are available to address HBP, many of which are low-cost generics. Nevertheless, a 2019 study found considerable problems with hypertension control and medication adherence.[49]

Existing hypertension treatments are inadequate, as many US adults have uncontrolled blood pressure and are not adherent, despite widespread efforts to educate about its dangers.

Continued innovation may help bring hypertension under control, thus helping reduce ASCVD in the process.

Approximately 19.4 million US adults are receiving pharmacological treatment for hypertension, but their blood pressure remains uncontrolled.[58] Additionally, the study authors estimate that nearly one-third (31%) of insured US adults being treated with antihypertensive medication (≈16.3 million people) were nonadherent, suggesting that existing treatments and interventions are insufficient.

The same study reported high nonadherence among insured adults aged 18 to 64 years, with estimates approaching 58% for adults aged 18 to 34 years and 47% for adults aged 35 to 44 years. The authors found this "concerning, as almost half of US adults being treated for hypertension are aged <65 years, and heart disease and stroke mortality rates are potentially increasing among this age group." Furthermore, the authors indicated that inadequately managed hypertension at young ages can adversely affect future cardiovascular health.[49]

There are opportunities to improve ASCVD outcomes

As we have seen, ASCVD has a high prevalence, with associated enormous economic and clinical costs. Additionally, it is undertreated, and people at high risk are being treated far too late. The fact that CVD is still the leading cause of death in the US should sound the warning that new treatment innovations are still desperately needed to address risk factors such as high blood cholesterol and hypertension. The more choices providers and patients have available to prevent and manage ASCVD, the better clinicians will be able to determine the best treatment.

- **Promote greater adoption of team-based care and patient education**
  The 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease includes a team-based approach among its top 10 take-home messages for the primary prevention of CVD.[4] Its researchers found a greater reduction of ASCVD risk with team-based care than with usual care in patients with hypertension, diabetes, and hyperlipidemia. A team-based approach to ASCVD prevention may result in significant improvements in patient outcomes and often meets patient needs better than standard care, especially in low-resource settings and among vulnerable populations. Additionally, researchers found that collaborative decisions are more likely to address potential barriers to treatment options compared with treatment and guidance offered without patient input.
- **Earlier and more testing could accelerate remediation measures**
  The 2018 AHA Guideline for the Management of Blood Cholesterol recommends earlier screening and earlier treatment.[22] Screening for hypercholesterolemia is recommended for children as young as 9 years old, even in the absence of a strong family history of CVD. The guideline also recommends that adults aged 20 years and older should have lipid panels every 4 to 6 years, beginning at age 21. The sooner patients at risk of ASCVD can be identified, the sooner remediation measures can be implemented.
- **Increasing access to intensive lipid-lowering therapeutics could lower LDL-C levels dramatically**
  Cardiovascular prevention guidelines recommend increasingly strict cholesterol targets for patients with ASCVD, as mounting evidence supports the benefit of progressively lower cholesterol. Guidelines also stress the importance of rapid attainment of targets to maximize the preventive benefit.[59] In other words, the goal for patients should be to reduce LDL-C levels "as much as possible and as fast as possible."[60]

  One of the most significant changes in the updated 2018 AHA Guideline for the Management of Blood Cholesterol is the stronger support for selective use of adjunct nonstatin medications for LDL-C reduction in patients with established ASCVD.[22]

  Lowering the UM and OOP cost barriers to powerful lipid-lowering medications described earlier will facilitate physicians' abilities to implement clinical treatment guidelines. Easing access to more intensive lipid-lowering medications would help reduce the number of major ASCVD events, such as MI, transient ischemic attack, and stroke, thereby reducing the burden of ASCVD on society and for patients.

- **Streamlining access to prescription drugs to facilitate prevention**

  Reduce/remove utilization management. A 2017 study analyzed the time required to comply with insurers' prior authorization requests. The authors demonstrated that the process of completing prior authorization forms (ranging from 2-6 pages of extensive paperwork), corresponding with insurance companies via telephone or email, writing appeal letters when needed, and communicating with patients throughout this process required 4 to 6 hours per patient.[61]

The long wait times for preauthorized medical care have adverse consequences for patients. A 2018 American Medical Association survey found that more than 9 in 10 physicians (92%) said the prior authorization process delays patient access to necessary care, and nearly 4 in 5 physicians (78%) report that prior authorization can sometimes, often, or always lead to patients abandoning a recommended course of treatment.[62]

> *"Emphasizing prevention as much as treatment would prevent a lot of heartbreak."*
>
> – Policy representative for a nonprofit organization devoted to diagnosis and management of ASCVD

To address this, attention is on developing standardized prior authorization forms that are universally applicable, reflect recommendations from the current guidelines, and also ensure that clinicians are held accountable for appropriate prescription patterns.[63]

Reduce/remove cost-sharing. Government agencies could also play a role in improving access to prescription drugs. A key provision of the Affordable Care Act is the requirement that private insurance plans cover recommended preventive services without any patient cost-sharing.[64] The required preventive services come from recommendations made by 4 expert medical and scientific bodies: the US Preventive Services Task Force (USPSTF), the Advisory Committee on Immunization Practices, the Health Resources and Services Administration's (HRSA) Bright Futures Project, and the Institute of Medicine's Committee on Women's Clinical Preventive Services.[65] The USPSTF has given a B rating for the use of aspirin and statins as a form of preventive medicine, mandating their use for subsets of adults.[66,67] A similar case could be made for the USPSTF to support the use of other medications for people at risk of ASCVD, such as those with HBP who cannot be managed through lifestyle changes or subsets of patients who see CVD progression even with the use of statins.

- **Coverage of coronary artery calcium testing to detect high ASCVD risk**

  Payers only cover screening for risk factors of ASCVD such as blood pressure and blood cholesterol; this approach tends to miss high-risk individuals and over-treat low-risk individuals.

  The 2018 AHA Guideline for the Management of Blood Cholesterol recommendeds coronary artery calcium measurement when the decision about starting statin therapy is uncertain from the patient or provider perspective.[22]

  Coronary artery calcium is measured noninvasively with a 5-minute computed tomography scan of the heart and costs less than $200. However, most payers do not cover it.

- **Pharmaceutical and medical innovation could reduce ASCVD prevalence**

  Providing additional choice and competition in the market conveys benefits in terms of clinical appropriateness, cost, and patient preferences. Perhaps the next advance could be regimens with longer half-lives, patches that offer controlled-release formulations, or other inventions that have not yet been imagined.

The payer mantra, "we don't pay for convenience," is often invoked as a defense against products with premium prices compared to those with similar safety and efficacy profiles. However, payers will pay if a product's more convenient dosing or method of administration translates to better adherence, so that offers an opportunity. Meeting the patient where they are at and ensuring the right treatment for the right patient could go a long way toward changing the ASCVD outlook in the US.

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