March 2017

AJMC® SUPPLEMENT
THE AMERICAN JOURNAL OF MANAGED CARE®

Unmet Needs in Cardiovascular Risk Reduction

CARDIOVASCULAR DISEASE OVERVIEW

Cardiovascular disease (CVD) poses a substantial burden on global health as the leading cause of deaths worldwide, accounting for over 17.3 million per year.[1] Diseases and conditions affecting the heart and vascular system fall under the umbrella of CVD. This article focuses on the treatment of high-risk patients with such CVDs as coronary heart disease (CHD), cerebrovascular disease, and hypertensive heart disease.

Atherosclerosis is a causative factor in CHD, cerebrovascular disease, and aortic and arterial diseases, including hypertension and peripheral vascular disease (PVD).[1] CHD is the narrowing of the blood vessels that supply blood and oxygen to the heart, and this may lead to unstable angina, myocardial infarction (MI), and heart failure (HF). Cerebrovascular disease, or ischemic stroke, occurs as a result of atherosclerosis, where lipid deposits obstruct circulation to the brain. Hypertensive heart disease is specific to the blood vessels and may include aneurysm, high blood pressure, and peripheral arterial disease (PAD). PAD is characterized by vascular proliferation and remodeling of the small pulmonary arteries, where these changes may result in a progressive increase in pulmonary vascular resistance, ultimately leading to HF and premature death.

Most risk factors for CVD are manageable with lifestyle modifications and effective treatment; however, genetic risk factors have been identified that predispose patients to CVD. Behavioral risk factors for CVD include smoking, sedentary lifestyle, and unhealthy diet; metabolic risk factors include hypertension, diabetes, elevated body weight, and raised blood cholesterol.

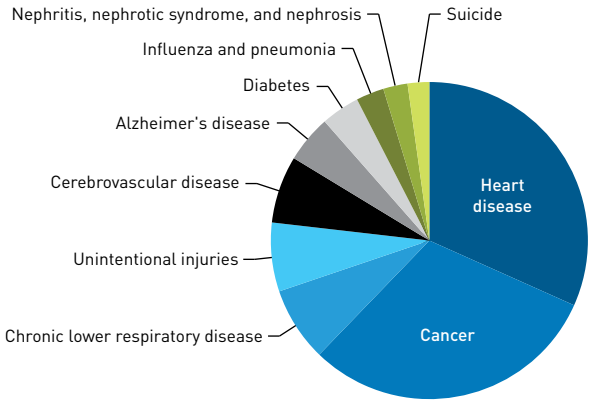
Control of lipid levels is one of the most effective strategies for cardiovascular (CV) event prevention.[1] Low-density lipoprotein cholesterol (LDL-C) plays an important role in arterial plaque development and progression of atherosclerosis in the pathogenesis of CV events. Circulating LDL-C molecules penetrate the arterial wall endothelium and become oxidized to promote inflammation. In turn, this causes injury to the overlying endothelium and smooth muscle cells, which promotes deposition of cholesterol in the arterial wall.[2] Elevations in LDL-C levels directly link to progression from early stage fatty streaks to advanced-stage lipid-rich plaques. Over time, vessels stiffen and atherosclerotic plaques can rupture, triggering thrombus formation in 1 or more coronary arteries. The resulting decreased myocardial blood flow and cardiomyocyte necrosis lead to CHD, MI, and cardiac death. Thrombus development in the brain as a result of atherosclerosis leads to stroke and PVD.[1,3]

The results of many clinical trials have demonstrated the efficacy of statins at reducing circulating LDL-C levels, primarily to reduce major CV events and related deaths. The evidence from these trials has been useful in designing cholesterol-lowering treatment targets and guidelines that aim to prevent and manage CVD. However, several clinical trials indicate that a large proportion of patients, particularly those at high or very high CV risk, fail to achieve lipid goals. Despite statin efficacy in achieving LDL-C targets, addressing residual CV risk (incidence of CV events in patients receiving statin treatment) is of great importance for the development of novel therapeutics that will reduce CV events.

BURDEN OF CVD IN THE UNITED STATES

Since 1918, CVD has been responsible for more American deaths than any other major cause of death, exceeding the mortality rates of cancer and chronic lower respiratory disease combined.[4] In fact, deaths due to CVD substantially contributed to the total number of American deaths compared with the other top 10 leading causes of death: cancer (22.5%); chronic lower respiratory disease (5.6%); unintentional

Figure 1. Leading Causes of Death and Number of Deaths in the United States, 2014[5]



injuries (5.2%); Alzheimer's disease (3.6%); diabetes (2.9%); influenza and pneumonia (2.1%); nephritis, nephrotic syndrome, and nephrosis (1.8%); and suicide (1.6%) (**Figure 1**[5] and **Table 1**[5]).[5] Approximately 2200 Americans die of CVD each day, which translates to an average of 1 death every 40 seconds.[4] Of the 2,626,418 all-cause deaths in the United States in 2014, CVD, including heart disease and cerebrovascular disease, accounted for 28.5% of them. In addition, CVD is associated with high morbidity, as CV events such as MI and stroke are associated with an increased risk of a recurrent event.[6]

An estimated 85.6 million American adults are living with 1 or more types of CVD,[4] and because the risk increases with age, CVD poses a tremendous burden on the elderly population. More than half (or 43.7 million individuals) of the population affected by CVD comprises adults 60 years and older.[4]

US Prevalence and Impact of MI and Stroke

CHD may manifest as an MI, which can be both an early predictor of CHD from the first coronary event or a causative factor in a recurrent event.[3] In 2012, of the estimated 15.5 million Americans living with CHD at that time, an initial or recurrent MI affected nearly half of that population (7.6 million). In the United States, an MI occurs approximately every 42 seconds, leading to 1 death every minute. In 2013, CHD was responsible for 370,213 US deaths, 116,793 of which were due to an MI; an additional 538,239 deaths were associated with a CHD comorbidity.[4]

Stroke posed a substantial burden to the United States as the fifth leading cause of death in 2014 (Figure 1[5] and Table 1[5]).[5] Approximately 795,000 Americans experience an ischemic or hemorrhagic stroke each year, with 185,000 having a recurrent stroke (second or subsequent stroke) and most (610,000) experiencing a first stroke. The impact of stroke on the US population translates to 1 stroke event every 40 seconds, leading to 1 stroke-related death every 4 minutes. In 2013, stroke was responsible for 1 out of every 20 deaths in the United States (**Table 2**[4]).[4]

Economic Burden of CVD

CVD is associated with a formidable economic burden in the United States, with both high direct medical costs, including hospital and medical resource use, and indirect costs stemming from productivity loss due to CVD-related premature deaths. From 2011 to 2012, direct and indirect CVD healthcare expenditures totaled $316.6 billion, representing a higher burden than any other diagnostic group (**Figure 2**[4], **Figure 3**[4], **Table 3**[4]).[4] It is estimated that of every $6 spent on healthcare in the United States, $1 is spent on treatment for CVD.[7] Of the total $193.1 billion CVD-related direct costs, the most substantial payments were for inpatients, with hospital stays totaling $90.1 billion and emergency department visits adding $7.6 billion. In contrast, outpatient care, including home healthcare and hospital or office provider visits, cost $62.6 billion. Additionally, prescription medication for the treatment of CVD totaled $32.8 billion.[4]

Despite substantial improvement in CVD outcomes with appropriate medical treatment, the high rates of hospital readmission and event recurrence contribute to the economic burden of CVD. Approximately 24% of patients with HF hospitalizations are readmitted within 30 days after discharge and over 50% of patients with HF are readmitted within 6 months of discharge. Although is it is difficult to predict the

Table 1. Leading Causes of Death and Number of Deaths in the United States, 2014[5]

Rank	Disease	Total Deaths	% Total Deaths[a]
1	Heart disease[b]	614,348	23.4%
2	Cancer	591,699	22.5%
3	Chronic lower respiratory disease	147,101	5.6%
4	Unintentional injuries	136,053	5.2%
5	Cerebrovascular disease[b]	133,103	5.1%
6	Alzheimer's disease	93,541	3.6%
7	Diabetes	76,488	2.9%
8	Influenza and pneumonia	55,227	2.1%
9	Nephritis, nephrotic syndrome, and nephrosis	48,146	1.8%
10	Suicide	42,773	1.6%
All-Cause Deaths = 2,626,418			
Total Cardiovascular Disease Deaths[b] = 747,451			

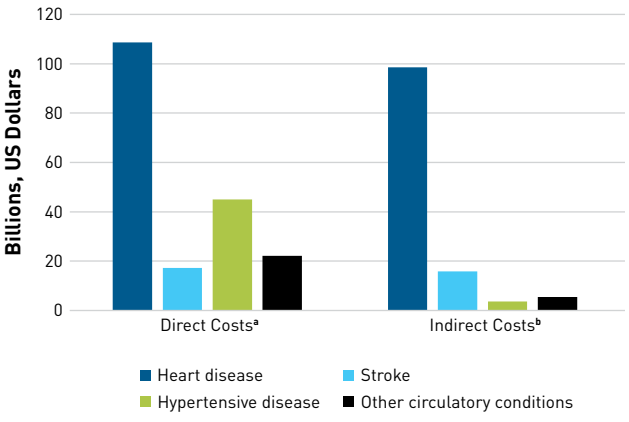
[a]Calculated by dividing total deaths by all-cause deaths.
[b]Includes deaths due to heart disease and cerebrovascular disease.

Table 2. Deaths Due to CVD, CHD, and Stroke in the United States[4]

	Number of Deaths
CVD	1 in every 3 deaths
CHD	1 in every 7 deaths
Stroke	1 in every 20 deaths

CHD indicates coronary heart disease; CVD, cardiovascular disease.

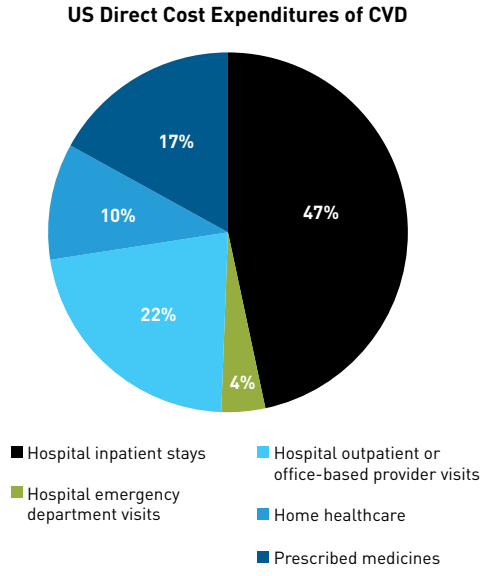
Figure 2. Direct Versus Indirect Costs of Heart Disease, Stroke, Hypertensive Disease, and Other Circulatory Conditions[4]



[a]Direct costs include hospital and medical resource use.

[b]Indirect costs include loss of productivity due to premature death from cardiovascular disease.

Figure 3. Breakdown of Direct Costs of Heart Disease (in US$ Billions)[4]



CVD indicates cardiovascular disease.

cause of CVD-related early readmissions due to the comorbidities and risk factors associated with CVD, it is estimated that up to 75% of early readmissions may be preventable.[8]

Mortality Burden of CVD

In an effort to reduce the mortality burden of CVD and stroke by 20% in the United States by 2020, the American Heart Association (AHA) addressed the need for behavior modification associated with cardiometabolic risk in their 2020 Impact Goal. Specific measurable targets of CV health improvements are outlined in 7 risk factor categories: blood pressure, physical activity, cholesterol, healthy diet, healthy weight, smoking cessation, and blood glucose.[4]

Deaths related to CVD and stroke decreased rapidly from 2000 to 2011, with an annual decline of 3.79% for all CVD, 3.69% for heart disease, and 4.53% for stroke. This substantial decline in mortality was associated with marked improvements in smoking prevalence, high cholesterol, and high blood pressure, and increased use of statins in at-risk patients. However, the decrease in CVD mortality substantially slowed from 2011 to 2014, averaging only 0.65% during those years.[9] Alarming increases in the prevalence of obesity and diabetes coupled with minimal changes in healthy diet scores and physical inactivity are unlikely to impact projected goals for CV health by 2020 despite overall declines in smoking and hypertension risk factors.[9,10] As a result, given substantial increases in the prevalence of behavioral risk factors, the AHA's 2020 Impact Goal is unlikely to be successful, indicating the continued threat of CVD on overall population health.

RISK FACTORS ASSOCIATED WITH CVD

Genetic Risks and Interaction With Lifestyle Factors

A higher risk of CVD is associated with a family history of most CVD conditions, including hypertension, stroke, type 2 diabetes (T2D), and hypercholesterolemia. Although genetic factors do not directly cause CVD, when coupled with lifestyle risk factors, they do affect an individual's susceptibility.[4] National Health and Nutrition Examination Survey (NHANES) data from 2009 to 2012 were analyzed to determine the associations among family history of diabetes, CVD, and lifestyle behaviors and risk factors (including smoking, low physical activity, excessive dietary sodium, and cholesterol intake and obesity) in a nationally representative sample of US adults (n = 20,293). Outcome measures of key lifestyle behaviors and risk factors included body mass index (BMI), smoking, physical activity, dietary sodium and cholesterol, and other variables. A family history of diabetes, CVD, or both was discovered in 42% of noninstitutionalized US adults (ie, adults not in prisons or nursing homes), which placed them in a high-risk category for the development or progression of both diseases. In addition, an exponential increase in cardiometabolic risk was found to be associated with a family history of diabetes, CVD, or both diseases, as well as obesity and smoking.[11]

Significant advancements in the field of genomics and genetic evaluation methods have allowed for better characterization of CVD and its associated risk factors. The effects of elevated LDL-C and triglyceride levels on CHD risk are most evident in individuals with familial forms of hyperlipidemia, as they often experience premature CHD

Table 3. Estimated Direct Costs Breakdown of CVD and Stroke: United States, Annual Average 2011-2012[4]

	Direct Costs (in US$ Billions)				
	Heart Disease	Stroke	Hypertensive Disease	Other Circulatory Conditions	Total CVD
Hospital inpatient stays	63.4	8.5	6.2	12.0	90.1
Hospital emergency department visits	4.7	0.9	1.4	0.6	7.6
Hospital outpatient or office-based provider visits	21.2	1.6	13.4	6.2	42.4
Home healthcare	8.8	4.8	5.0	1.6	20.2
Prescribed medicines	10.6	1.4	19.0	1.8	32.8
Total expenditures	108.7	17.2	45.0	22.2	193.1

CVD indicates cardiovascular disease.

despite lacking significant risk factors, such as obesity, hypertension, and smoking.[12] Among those with elevated LDL-C who have no form of familial hyperlipidemia, genome-wide association studies have determined that the risks for elevated LDL-C can be attributed to single nucleotide polymorphisms and variations in the genes encoding the LDL receptor (*LDLR*), apolipoprotein B, and proprotein convertase subtilisin/kexin type 9 (*PCSK9*), among other genes, which lead to increases in circulating LDL-C levels.[2]

Aging

It is estimated that by 2030, nearly a quarter of the US population will be 65 years and older, underlining the importance of recognizing aging as an unavoidable risk factor for CVD[13]; 82% of all CVD-related deaths occur in adults 65 years and older. Physiologic age-related changes to the CV tissues lead to this enhanced CVD risk. Over time, marked cellular changes, such as senescence, accumulation of damage, and loss of regenerative capacity lead to dysfunctional vasculature, including thickening of arteries and fibrosis. In this way, the aging population is more susceptible to such CVD conditions as atherosclerosis, CHD, hypertension, MI, atrial fibrillation, HF, and stroke.[13]

Modifiable Risk Factors

Obesity and excess weight contribute to physical inactivity, hypertension, hyperlipidemia, and diabetes—factors that cumulatively place individuals at risk for CVD. Approximately 80% of CVD can be prevented with lifestyle changes, such as smoking cessation and maintaining a healthy weight through diet and physical activity.[4] In fact, modifiable CV risk is associated with several lifestyle factors that can be changed through behavioral modifications to diet and activity levels to control high blood pressure, diabetes, and elevated lipid levels.[14]

Body Weight and Obesity

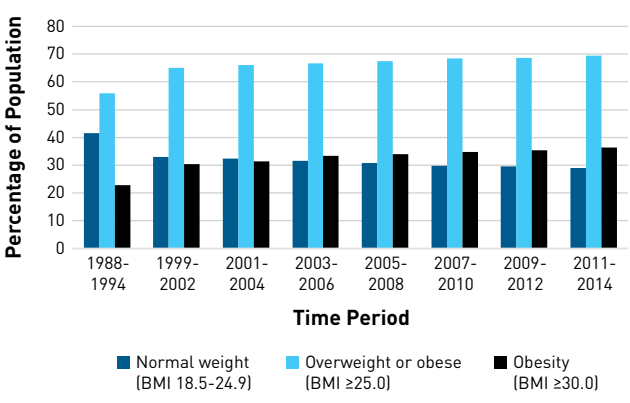
In 2012, 159.2 million Americans were overweight or obese (BMI >25.0 kg/m^2).[4] In addition, the prevalence of adult obesity substantially increased from an average of 22.9% between 1988 and 1994 to 36.4% between 2011 and 2014 (**Figure 4**[5]).[5] During the same time period, a similar rate of increase was observed in the percentage of US adults classified as overweight, along with a decline in the percentage of adults with a normal BMI.[5]

Achieving a normal BMI, reducing blood pressure and LDL-C levels, and raising high-density lipoprotein cholesterol (HDL-C) levels can be accomplished by eating a healthy diet rich in fruits, vegetables, and low-fat dairy products, and small amounts of simple carbohydrates and saturated and total fats.[15] The benefits of a healthy diet and physical activity have been shown through observational studies that have explored CVD incidence and mortality.[14] It has been shown that a 22-lb weight loss can result in a 20% increase in HDL-C levels. In addition, aerobic physical activity, such as brisk walking at least 30 minutes per day for more than 3 days each week, can result in a 4 to 9 mm Hg blood pressure reduction and a 5% to 10% elevation in HDL-C levels.[15]

Diabetes

From 1990 to 2014, the prevalence of T2D more than tripled in the United States despite the disease being recognized as one of the strongest modifiable risk factors for CVD, including PAD, stroke, HF, atrial fibrillation, and CHD.[4,16] An estimated 21.1 million adults have been diagnosed with diabetes and an additional 8.1 million adults have diabetes but have not yet been diagnosed. This tremendous burden, including diabetes' association as a CVD risk factor, is expected to increase due to the 80.8 million adults who have prediabetes (having a fasting blood glucose between 100-126 mg/dL).[4]

Figure 4. Obesity Trends From 1994-2014 in US Adults 20 Years and Older (Percentage of Population)[5]



BMI indicates body mass index.

Diabetes is often clustered with other CVD risk factors: 70% to 80% of patients with T2D have elevated LDL-C levels, 60% to 70% are obese, and 75% to 85% have hypertension—all factors that put this population at an especially high risk for atherosclerotic disease. Heart disease mortality among adults with diabetes is 2 to 4 times higher than among adults without this modifiable risk factor. Much like other CVD risk factors, diabetes significantly contributes to the high risk of CV and cerebrovascular events among the aging population: at least 68% of adults with diabetes who are 65 years and older die from heart disease and 16% die from stroke.[4]

Hypertension

Approximately 80 million Americans have hypertension, which is associated with increased mortality and more years lived with CVD.[4] The risk factors associated with MI and stroke include hyperlipidemia, obesity, and smoking.

Approximately 77% of Americans who experience an incident stroke have uncontrolled high blood pressure, defined as an average systolic blood pressure of 140 mm Hg or higher and an average diastolic pressure of 90 mm Hg or higher.[4,5] A meta-analysis of 61 prospective observational studies of blood pressure and mortality discovered a correlation between increased blood pressure and CVD risk: among patients with a diastolic blood pressure above 115/75 mm Hg, each 20 mm Hg systolic blood pressure increase or 10 mm Hg diastolic blood pressure increase was associated with a 2-fold increase in mortality due to stroke and CHD.[17]

Tobacco Use

Cigarette smoking is the largest preventable cause of death and disease in the United States: 1 in every 3 deaths from CVD are due to smoking.[18] Although smoking is a risk factor for CVD on its own, it also directly contributes to additional CVD conditions and major risk factors for CVD, such as hypertension and hyperlipidemia.[4] Smoking creates endothelial cell injury and dysfunction, stimulating an inflammatory environment and arterial dilation that leads to vasculature narrowing. This accelerates the development of such CVDs as atherosclerosis, CHD, and stroke.[18]

CVD risk is directly proportional to the number of cigarettes smoked; therefore, high-volume smokers have the greatest CVD risk.[18] Further, current smokers are 2 to 4 times more likely to have a stroke compared with nonsmokers or those who quit smoking over 10 years ago,[4] approximately 7000 annual deaths could be prevented from a 5% increase in smoking cessation rates.[14] Smoking cessation represents a key action that has the potential for an exponential decrease in overall CVD risk. Stopping smoking has been reported to raise HDL-C by 4 mg/dL and to return this very important health statistic to nonsmoking levels.[15] Although smoking prevalence is decreasing, 19% of males and 15% of women in the United States are current smokers.[4]

Dyslipidemia and Elevated LDL-C Levels

The relationship between elevations in circulating LDL-C and CV risk is well established, indicating that LDL-C level is an independent predictor of CVD risk.[2] NHANES data from 2009 to 2012 indicate that an estimated 73.5 million Americans (31.7%) at least 20 years of age had a LDL-C level above 130 mg/dL.[4] And in the Atherosclerosis Risk in Communities study, the risk of an incident CHD event was elevated by approximately 40% for every 39 mg/dL increase in LDL-C. Due to the prevalence of this risk factor in the United States, the mainstay of efforts to improve lipid profiles in patients at risk for CVD is to lower LDL-C levels. However, between 2005 and 2008, less than half (34 million) of this large affected population received LDL-C-lowering therapy[17] and only 29.5% achieved controlled LDL-C levels.[4]

Because treatment to lower the LDL-C level is not always sufficient to prevent CHD in at-risk patients or to manage existing atherosclerosis, it is also important to evaluate and manage the HDL-C level. A low HDL-C level is an accepted risk factor of, and treatment target for, CHD, according to guidelines from the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III). HDL-C concentrations less than 40 mg/dL in men and less than 50 mg/dL in women are associated with greater CV risk.

The role of high-density lipoproteins (HDLs) is opposite that of low-density lipoproteins (LDLs) in the pathogenesis of CVD: HDLs facilitate cholesterol transport from peripheral areas in the body to the liver,[19] have the potential to reduce CV risk through anti-inflammatory and antioxidant activity, and display anti-apoptotic and anti-thrombotic effects. They have an inverse effect on CVD risk: an increase in HDL-C levels is associated with a decrease in CVD risk.[20] In fact, for every 1 mg/dL increase in HDL-C level, CVD risk is estimated to decrease by 2% to 3%.[15] However, 19.9% of American adults age 20 and older (44.6 million) have low HDL-C levels (<40 mg/dL).[4] The Veterans Affairs High-Density Lipoprotein Intervention Trial showed that increasing HDL-C levels and lowering triglycerides in patients with coronary artery disease whose primary lipid abnormality was a low HDL-C level significantly reduced the rate of a coronary event, thereby supporting the cardioprotective role of HDL-C.

LIPID-LOWERING THERAPY FOR CVD

Statins

The comprehensive management of dyslipidemia requires addressing such modifiable risk factors as hypertension, diabetes, obesity, and cigarette smoking, as well as controlling lipid levels. In that vein, the NCEP ATP III provided guidelines on treatment goals with statin or lipid-modifying therapy for lowering LDL-C to optimal levels: patients at high risk are those with 2 or more risk factors and CHD or noncoronary atherosclerotic disease risk equivalents, such as PAD. Patients at very high risk have established CVD and 1 or more additional risk factors, such as smoking, an elevated HDL-C level, hypertension, or a family history of CHD.[21] The goal for high-risk patients on statin therapy is an LDL-C level less than 100 mg/dL, while for very-high-risk patients, the goal is less than 70 mg/dL.[21,22]

More than 2 decades of clinical trial evidence have demonstrated the efficacy of statin therapy for modulation of cholesterol levels for primary and secondary prevention of atherosclerotic CV events, including stroke.[15] Statins induce favorable alterations in the composition of atherosclerotic plaques and may slow disease progression and the burden of CVD by reducing LDL-C levels.

The liver regulates circulating LDL-C concentrations via receptor-mediated endocytosis carried out by hepatic cell surface LDL receptors, and statins reduce circulating LDL-C levels through direct inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, a crucial enzyme responsible for cholesterol synthesis. First, statins decrease the production of intracellular cholesterol by inhibiting the biosynthetic rate-limiting step and inducing sterol regulatory element-binding protein 2-mediated upregulation of *LDLR* gene transcription. As a result, greater production and expression of LDL receptors at the surface of hepatocytes facilitate enhanced LDL-C binding and clearance from circulation and cholesterol recycling through receptor-mediated endocytosis. Statins may also exert therapeutic efficacy by increasing HDL-C levels and inhibiting triglycerides.[2,23,24]

Statins have been shown to decrease LDL-C levels by 21% to 55% depending on baseline lipid level and dosage.[21] The 2013 American College of Cardiology (ACC)/AHA cholesterol guideline panel found that statins proved to be the most effective and safe strategy for lowering LDL-C levels to reduce the risk of CVD.[21,25] The results of a meta-analysis evaluating data across 14 trials of patients treated with statins showed a 21% risk reduction of CV events for every 39 mg/dL drop in LDL-C level.[15] Currently, there are 7 statin monotherapies that have been approved by the FDA: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.[21]

Residual Risk of CV Events

The results of several studies have indicated that achieving an LDL-C level below 70 mg/dL is a challenge with statin therapy, as patients with symptomatic atherosclerosis are often unable to reach their LDL-C goals, despite maximally tolerated lipid-lowering therapy with statins. Data from several large prospective studies indicate that even in patients who achieve significant LDL-C reductions with intensive statin therapy, a high risk of CVD remains—and this is referred to as residual risk.

Residual CV risk in patients treated with statins is particularly high among those with diabetes. According to the NCEP ATP III and the American Diabetes Association/ACC Consensus Statement, patients with diabetes alone should be considered high risk.[21]

A meta-analysis of data from 18,686 patients with diabetes in 14 randomized trials showed that statin therapy was associated with a 21% reduction in major vascular events, a percentage similar to that observed in those without diabetes ($P < .0001$). Although statin therapy reduced the risk of a major vascular event compared with placebo per 1 mmol/L reduction in LDL-C level in patients with diabetes, the residual CV risk in these patients was higher than that in patients without diabetes (15.6% vs 13.7%, respectively). Overall, patients with diabetes treated with statins had an 8.3% rate of major coronary events compared with 7.2% in those without diabetes, and stroke occurred at an incidence of 4.4% compared with 2.7%, respectively.[26]

Another meta-analysis evaluated the lipid-lowering efficacy of intensive statin therapy and CV risk reduction. Among the 38,153 patients receiving statin therapy, 18,677 received 80 mg of atorvastatin or 20 mg of rosuvastatin. More than 40% of the high-risk patients in the analysis did not reach their LDL-C target of less than 70 mg/dL and 78.3% did not reach their LDL-C target of less than 50 mg/dL. Overall, 5387 patients (14.1%) developed at least 1 major CV event, which was defined as MI, fatal CHD, stroke, or hospitalization for unstable angina.[27]

The residual risk of CV events was apparent in the high-risk patients who did reach the recommended LDL-C level of less than 70 mg/dL. Patients achieving an LDL-C level less than 50 mg/dL had the lowest risk of major CV events (4.4%) compared with patients who achieved the recommended LDL-C level between 50 and 75 mg/dL (11.4%) and those who did not reach the goal of 75 to 100 mg/dL (16.5%).[27]

A retrospective analysis used NHANES data from 2007 to 2008 to evaluate lipid profiles among 35.5 million adults treated with lipid-modifying therapy: 10.4 million high-risk patients with CHD or CHD risk-equivalents were treated with statin monotherapy for more than 90 days. Among these patients, 24.0% achieved the recommended LDL-C level of less than 70 mg/dL and 76.8% met the goal of less than 100 mg/dL. Of patients achieving the LDL-C goal of less than 70 mg/dL, 38% had low HDL-C levels compared with 46% of those not at goal.[22]

Another retrospective study evaluated the lipid profiles of nearly 20,000 patients who received statin therapy, specifically assessing the occurrence of CV and cerebrovascular events, such as MI and ischemic stroke, during 2 years of follow-up. Statin therapy was found to be inefficient for reaching the LDL-C goal of less than 100 mg/dL in 34.4% of the study population. In addition, among the total population, statin therapy was ineffective at preventing CV or cerebrovascular events in 11.0% of patients. Of the patients with elevated LDL-C levels despite statin therapy, 10.5% of patients had cerebrovascular and CV events, 8.7% experienced an MI, 10.9% had revascularization, and 19.6% experienced a fatal or nonfatal stroke. Patients with elevated LDL-C levels represented only 33% of all patients included in the study who experienced a vascular event, indicating that the remaining 67% of patients who experienced vascular events achieved target LDL-C levels with statin therapy. Interestingly, patients taking statin therapy who experienced CV events were obese, had a history of smoking and diabetes, and were significantly older. This study demonstrated the occurrence of CV events despite statin therapy for LDL-C level reduction, highlighting the need for effective strategies to combat residual CV risk with statin therapy.[28]

The Scandinavian Simvastatin Survival Study evaluated simvastatin treatment compared with placebo in 4444 patients with a history of CHD, MI or angina pectoris, and high levels of LDL-C (100-144 mg/dL). A significant reduction in CV events was observed with statin treatment compared with placebo: over a median of 5.4 years, 28% of patients given placebo had 1 or more major coronary events, including MI and cardiac arrest, compared with a 19% CV event rate in those given statins. Major coronary events were higher in the patient cohort 60 years and older: 21% of these patients who received statins experienced 1 or more coronary events compared with 28.3% of patients who received placebo.[29]

The Treating to New Targets trial evaluated the LDL-C–lowering efficacy of intensive high-dose atorvastatin (80 mg once daily) compared with low-dose statin treatment (10 mg). A total of 10,001 patients with clinical CHD, a history of MI or atherosclerotic CHD, and a history of coronary revascularization were enrolled. Of these patients, 76.7% were current or former smokers, approximately half had hypertension, and 15% had a history of diabetes, in addition to BMIs indicating they were overweight or obese—all additional CVD risk factors.

Treatment with the 80-mg dose lowered LDL-C to a mean 77 mg/dL, whereas those receiving the 10-mg dose ended up with an average LDL-C level of 101 mg/dL. Despite this reduction of LDL-C levels, 8.7% of the patients treated with the 80-mg dose of atorvastatin experienced a major CV event defined as death from CHD, nonfatal MI, resuscitation after cardiac arrest, or a cerebrovascular event (fatal or nonfatal stroke). Those treated with the 10-mg dose had lesser reductions in LDL-C levels compared with patients receiving the 80-mg dose, but the risk of a CV event was still 10.9%.[30]

The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 trial enrolled 4162 patients hospitalized for acute coronary syndrome, defined as acute MI or high-risk unstable angina. Patients had numerous CVD risk factors, including diabetes (17.5%), hypertension (approximately 50%), and being current smokers (37%). Intensive therapy with atorvastatin 80 mg effectively lowered patients' median LDL-C level to 62 mg/dL compared with a reduction to 95 mg/dL with standard-dose pravastatin. Although treatment with 80 mg of atorvastatin reduced the risk of CV events (defined as death from any cause, MI, documented unstable angina requiring hospitalization, and revascularization requiring percutaneous coronary intervention) compared with the pravastatin group, a CV event rate of 22.4% indicated residual risk of death or a major CV event up to 2 years after intensive statin therapy. Additionally, 1 stroke event occurred within the 2 year follow-up for each treatment group, indicating that intensive therapy did not lead to a reduction in stroke risk compared with standard-dose therapy.[31]

The Incremental Decrease in Endpoints through Aggressive Lipid Lowering trial randomized 4533 patients with a history of MI to treatment with 80-mg atorvastatin or 20-mg simvastatin. In addition to MI history, 8.5% of patients had cerebrovascular disease, 4.4% had PVD, 5.5% had congestive HF, nearly 80% of the total patient population were current or former smokers, approximately 12% had a history of diabetes, and 33% had hypertension. At 1 year of follow-up, intensive statin treatment with atorvastatin reduced mean LDL-C to 79.1 mg/dL compared with 102 mg/dL with simvastatin. At the 5-year follow-up mark, atorvastatin treatment lowered the mean LDL-C level to 80 mg/dL compared with 98 mg/dL in patients treated with simvastatin.

Overall, treatment with intensive therapy did not significantly reduce CV mortality. At a median follow-up of 4.8 years, patients treated with atorvastatin had a 12% incidence of major CV events, while those receiving simvastatin experienced CV events at a rate of 13.7%. These results demonstrated that compared with standard-dose simvastatin, intensive therapy with atorvastatin did not significantly reduce CV events (eg, stroke, fatal CHD, nonfatal MI, or cardiac arrest with resuscitation, hospitalization of new or recurrent PAD and unstable angina).[32]

These studies highlight that a large population of patients fail to achieve the lipid targets suggested by current guidelines and that insufficient control of LDL-C levels in these patients leaves them susceptible to an increased risk of CV events.

PCSK9 Inhibitors

PCSK9 inhibitors are a novel strategy for reducing LDL-C levels in patients at high risk of CV events. They offer a solution to the unmet need for a statin alternative. PCSK9 inhibitors are fully humanized monoclonal antibodies to the PCSK9 protein, which functions in the upregulation of circulating LDL-C by decreasing LDL receptor expression. Normally, PCSK9 binds to the LDL-C/LDL receptor complex on the surface of hepatocytes and facilitates lysosomal catabolism of LDLR. PCSK9 inhibitors sequester PCSK9 to block PCSK9-mediated LDL receptor degradation, increase the availability of LDLR, and allow LDL-C to be removed from circulation.[33]

Currently, 2 PCSK9 inhibitors are indicated for the treatment of adults with atherosclerotic CVD or heterozygous familial hypercholesterolemia who require LDL-C reduction as an adjunct to diet and maximally tolerated statin therapy. Alirocumab received FDA approval in July 2015 and evolocumab in August 2015. Unlike alirocumab, evolocumab is indicated for patients with homozygous familial hypercholesterolemia as an adjunct to diet and other LDL-C–lowering therapies (statin, ezetimibe, LDL apheresis) to further reduce LDL-C levels. PCSK9 inhibitors are administered as subcutaneous injections monthly or bimonthly, while statins are typically administered orally once daily.[23,24,34-39]

Several trials have been conducted to evaluate the lipid-lowering efficacy of alirocumab and evolocumab with respect to CVD risk reduction when added to other lipid-lowering therapy. In the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY-Long Term) trial, patients were randomized 2:1 to alirocumab or placebo every 2 weeks for 78 weeks in addition to background statin and lipid-lowering therapy. Enrolled patients had established CHD or CHD risk equivalents, heterozygous familial hypercholesterolemia, or T2D with 2 or more CVD risk factors. Patients enrolled had uncontrolled hypercholesterolemia with a baseline mean LDL-C of 122 mg/dL. At baseline, 99% of the study population received background statin therapy (47% treated with high-dose therapy).[40]

The primary efficacy end point was the percent change in calculated LDL-C level from baseline to week 24. Patients treated with alirocumab achieved a 61.9% reduction in LDL-C from baseline compared with placebo (95% CI, −64.3% to −59.4%; P <.001). Alirocumab successfully reduced LDL-C levels to a mean 48.3 mg/dL compared with 118.9 mg/dL in placebo-treated patients. Additionally, a significantly (P <.001) higher proportion of patients in the alirocumab treatment group achieved the target LDL-C level of less than 70 mg/dL (79.3%) compared with the placebo group (8.0%). After 78 weeks of treatment, patients treated with alirocumab achieved a 56% reduction in LDL-C from baseline compared with patients treated with placebo (95% CI, −59.1% to −52.8%; P <.001). Alirocumab reduced LDL-C levels to a mean 57.9 mg/dL compared with 122.6 mg/dL in placebo-treated patients.[40]

Investigators noted statistically significant between-group differences in the CV event rate, which included death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, and hospitalization due to unstable angina. The CV event rate was 1.7% with alirocumab and 3.3% with placebo (P =.02). Importantly, statistically significant differences in the rate of CV events were not observed between treatment groups when the outcomes of HF hospitalizations and coronary revascularization driven by ischemia were included in the analysis. The rates

of CV events were similar across treatment arms, with these events included: 4.6% in the alirocumab arm and 5.1% in the placebo arm. The incidence of adverse events (AEs) was similar across both treatment groups at 81.0% in the alirocumab group and 82.5% with placebo. AEs that occurred more frequently with alirocumab treatment than with placebo included general allergic reaction (10.1% vs 9.5%), injection-site reactions (5.9% vs 4.2%), myalgia (5.4% vs 2.9%), neurocognitive disorders (1.2% vs 0.5%), and ophthalmologic events (2.9% vs 1.9%). A total of 7.2% of alirocumab-treated patients and 5.8% of placebo-treated patients discontinued study treatment due to an AE.[40]

Evolocumab has also been evaluated as an adjunct to standard lipid-lowering therapy in clinical trials. A combined analysis of data from the Open-Label Study of Long-term Evaluation Against LDL-C (OSLER)-1 and OSLER-2 trials demonstrated that over a median treatment duration of 11.1 months, more patients treated with evolocumab and standard lipid-lowering therapy achieved target LDL-C levels and experienced improved CV event outcomes compared with patients who received standard therapy alone. A total of 74.1% of eligible patients from OSLER-1 and OSLER-2 were randomized 2:1 to receive extended therapy with evolocumab (420 mg monthly or 140 mg evolocumab every 2 weeks) as an adjunct to standard therapy or background therapy alone. Background lipid-lowering therapy consisted of statins in 70.1% of patients (27.1% received high-intensity statin treatment) and ezetimibe in 13.5% of patients. Importantly, across both trials, 80.4% of the population had at least 1 CVD risk factor and 45.4% were at moderate to high or high risk of CV events as determined by National Cholesterol Education Program criteria.[41]

The median baseline LDL-C level in the OSLER-1 and OSLER-2 study populations was 120 mg/dL; the relative LDL-C reduction was evaluated across the 48-week treatment period as the percent change in the LDL-C level from baseline (the secondary end point of the OSLER trials). As part of the extension study, LDL-C levels were evaluated after 12 weeks of study treatment. Evolocumab treatment significantly ($P < .001$) reduced LDL-C levels by 60.9% from baseline compared with the reduction with standard therapy. Evolocumab maintained LDL-C reductions throughout the study treatment period; evolocumab-treated patients achieved a relative reduction of 58.4% in LDL-C levels compared with those treated with standard therapy alone after 48 weeks of study treatment ($P < .001$).[41] At the 52-week end point of the OSLER-1 trial, 62.5% of evolocumab-treated patients achieved LDL-C levels less than 70 mg/dL compared with 1% of patients treated with standard therapy alone.[42]

Evolocumab in addition to standard therapy reduced the rate of all CV events compared with standard therapy alone. In the OSLER trials, adverse CV events evaluated by the investigators included CV death or unknown cause; coronary events such as MI, unstable angina requiring hospitalization, or coronary revascularization; cerebrovascular events (stroke or transient ischemic attack); and HF requiring hospitalization. Investigators evaluated CV events in an exploratory analysis. At least 1 CV event occurred in 29 of 2976 patients treated with evolocumab and 31 of 1489 patients treated with standard therapy alone. There was a significantly lower 52-week CV event rate with evolocumab compared with placebo (0.95% vs 2.18%; $P = .003$; HR, 0.47). The rate of AEs (primary end point of both OSLER trials) was 69.2% with evolocumab and 64.8% with standard therapy. The addition of evolocumab to standard therapy was not associated with an increase in the overall rate of serious AEs (7.5% in both treatment groups). Injection-site reactions were reported in 4.3% of evolocumab-treated patients and were not observed in the standard therapy group. Serious AEs led to evolocumab discontinuation in 2.4% of patients, but there were no treatment discontinuations due to serious AEs in the placebeo group.[41]

Additional trials investigating long-term CV outcomes are necessary to further establish the benefit of LDL-C lowering achieved with evolocumab and alirocumab with respect to further CVD risk reduction when added to other lipid-lowering therapy.

CONCLUSION

CVD poses a tremendous healthcare burden nationally and globally. In the United States, CVD is the leading cause of death. Therefore, controlling CVD risk is a key population health initiative in the United States. Statins, the current treatment standard for CVD, have been shown to reduce CVD risk. However, residual risk has been established in numerous clinical trials of statin therapy.

The Triple Aim of healthcare (ie, improving the experience of care, improving the health of populations, and reducing the costs of healthcare) defines the National Quality Strategy, which focuses on 6 priorities in the quality of care, one of which focuses on promoting the most effective prevention and treatment practices for the leading causes of death, particularly CVD.[43] The unmet needs of improving outcomes and promoting a healthy lifestyle in at-risk patients have become a central focus of the national movement for increased quality and better outcomes in healthcare. With the prevalence of CVD increasing along with many of the modifiable risk factors for CVD, novel therapies, including the current trend of precision medicine, are needed to reduce the risk of CVD in conjunction with lifestyle modifications. •

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