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Review Articles

A review of low-density lipoprotein cholesterol, treatment strategies, and its impact on cardiovascular disease morbidity and mortality

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Abstract: Cardiovascular (CV) disease is a leading cause of death worldwide, accounting for approximately 31.4% of deaths globally in 2012. It is estimated that, from 1980 to 2000, reduction in total cholesterol accounted for a 33% decrease in coronary heart disease (CHD) deaths in the United States. In other developed countries, similar decreases in CHD deaths (ranging from 19%–46%) have been attributed to reduction in total cholesterol. Low-density lipoprotein cholesterol (LDL-C) has now largely replaced total cholesterol as a risk marker and the primary treatment target for hyperlipidemia. Reduction in LDL-C levels by statin-based therapies has been demonstrated to result in a reduction in the risk of nonfatal CV events and mortality in a continuous and graded manner over a wide range of baseline risk and LDL-C levels. This article provides a review of (1) the relationship between LDL-C and CV risk from a biologic, epidemiologic, and genetic standpoint; (2) evidence-based strategies for LDL-C lowering; (3) lipid-management guidelines; (4) new strategies to further reduce CV risk through LDL-C lowering; and (5) population-level and health-system initiatives aimed at identifying, treating, and lowering lifetime LDL-C exposure.

Introduction

Cardiovascular (CV) disease is the leading cause of mortality worldwide, accounting for 31.4% of deaths in 2012.[1] In developed countries, age-adjusted CV mortality rates are declining, but CV disease remains the leading cause of mortality due to rapid aging of the population. In low-income to middle-income countries, both age-adjusted CV mortality rates and aging of these populations are contributing to a rapid increase in CV mortality.[2] Data from 2010 demonstrate that CV disease accounted for 31.9% of US deaths, with ischemic heart disease and stroke accounting for the vast majority (total 27.6%; 21.1%, and 6.5%, respectively). In the United States, the resultant direct and indirect annual costs were estimated to be $240.9 billion.[3,4]

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The global cost of CV disease was estimated to be $863 billion in 2010, with a 22% increase expected by 2030.[5]

A large, worldwide study found that among all modifiable risk factors, abnormal lipid levels were associated with the highest population attributable risk (approximately 50%) for the occurrence of myocardial infarction (MI; Table 1).[6]

This is due to their prevalence and strong, independent association with the risk of MI. In western countries, lifestyle interventions and evidence-based therapies, including those focused on hypercholesterolemia, have led to a reduction in CV risk on a population level. In a series of studies covering the 1980 to 2010 time period in the United States, Canada, and Europe (Table 2), it was estimated that 19%–46% of the total reduction in the rate of coronary heart disease (CHD) mortality was explained by a reduction in total cholesterol levels attributed to lifestyle changes and pharmacologic treatment.[7–16]

Low-density lipoprotein cholesterol (LDL-C) has now largely replaced total cholesterol as the primary lipid measurement for evaluation of risk due to atherogenic lipoproteins. LDL-C is a measure of the total cholesterol content of LDL particles, reflecting both the number of LDL particles and their individual cholesterol content. Most current guidelines include LDL-C as a primary target for initiating and adjusting lipid-lowering interventions.[17–20]

In addition, more effective and/or scalable LDL-C reduction strategies are under investigation for risk reduction in both primary and secondary prevention. This article provides a review of (1) the relationship between LDL-C and CV risk from a biologic, epidemiologic, and genetic standpoint; (2) evidence-based strategies for LDL-C lowering; (3) lipid-management guidelines; (4) new strategies to further reduce CV risk through LDL-C lowering; and (5) population level and health-system initiatives aimed at identifying, treating, and lowering lifetime LDL-C exposure.

Table 1 Population attributable risk for the incidence of acute MI for modifiable risk factors*

Risk factor	Population attributable risk (%)‡
Abnormal lipids†	49.2
Tobacco consumption (current smoker)	35.7
Psychosocial	32.5
Abdominal obesity	20.1
Hypertension	17.9
Diet (lack of daily vegetable and fruits)	13.7
Physical activity	12.2
Diabetes	9.9
Alcohol intake	6.7

Apo, apolipoprotein.
*Based on the INTERHEART study by Yusuf et al., 2004.[6]
†Estimated by apoB/apoA1 ratio (fifth quintile compared to first).
‡Population attributable risk percentages do not add up to 100% for a combination of risk factors, because an MI can be simultaneously attributed to >1 risk factor and thus be counted twice.

Relationship between LDL and CV risk

Cholesterol is circulated in the body's aqueous extracellular environment by 5 major types of lipoprotein (chylomicrons, very low-density lipoprotein [VLDL], intermediate-density lipoprotein [IDL], LDL, and high-density lipoprotein [HDL]). The liver serves as the key organ for cholesterol metabolism and regulation of plasma levels of cholesterol. The process of LDL formation begins when intrahepatic cholesterol, either from gut absorption or *de novo* synthesis, is repackaged by the liver (along with proteins, triglycerides, and phospholipids) into VLDL. VLDL then enters the circulation and is converted by lipoprotein lipase and cholesteryl ester transfer protein (CETP) into more cholesterol-enriched species, first IDL and then LDL. The liver regulates the concentration of these circulating lipoprotein species primarily by their clearance through LDL receptors on the hepatic surface.[21]

Circulating LDL particles are able to penetrate the endothelium of arterial walls and become oxidized, promote inflammation, and drive injury to the overlying endothelium and surrounding smooth muscle cells.[22] Persistent elevations in circulating LDL-C have been directly linked to progression from early-stage fatty streaks to advanced-stage, lipid-rich plaques. For example, LDL receptor-deficient mice (i.e., unable to clear LDL from the circulation) have elevated LDL-C and consequently develop severe atherosclerosis.[23] Conversely, mice with virtually no LDL-C do not develop atherosclerosis irrespective of diet and other CHD risk factors.[24]

Epidemiologic investigations have validated LDL-C as an independent predictor of CV risk. The Framingham Heart Study demonstrated that men and women were >1.5 times more likely to develop clinically significant CHD if their LDL-C was >160 mg/dL compared to a reference population with LDL-C <130 mg/dL.[25] In the Atherosclerosis Risk in Communities (ARIC) study, the risk of an incident CHD event was elevated by approximately 40% for every 39 mg/dL incremental increase in LDL-C.[26]

Genetic analyses have demonstrated that a number of single-nucleotide polymorphisms (SNPs) are associated with LDL-C and CV risk. A study by Willer et al. demonstrated that SNPs of genes such as *PCSK9*, *APOE*, *APOB*, and *LDLR* that result in elevated LDL-C are also associated with elevated CV risk.[27] Another study by Kathiresan et al. demonstrated that specific SNPs of genes such as *PCSK9, APOE, APOB, HMGCR,* and *LDLR* result in decreased LDL-C and are associated with decreased CV risk.[28] These associations have been validated in other investigations.[29–32]

Genetic studies suggest that CV risk is associated not just with the absolute concentration of LDL-C but also with the duration of exposure. Certain genetic mutations

Table 2 Studies assessing the attributable risk reduction in CHD mortality driven by statins and other changes affecting total cholesterol levels

Study	Country	Time period	Attributable risk reduction* (%)		
			Statin treatment	Other causes	Total
Bjorck et al., 2009[7]	Sweden	1986–2002	6.2	39.5	45.7
Bandosz et al., 2012[8]	Poland	1991–2005	3.4	39.0	42.4
Wijeysundera et al., 2010[9]	Canada	1994–2005	15.4	22.8	38.2
Flores-Mateo et al., 2011[10]	Spain	1988–2005	5.6	31.1	36.7
Hughes et al., 2013[11]	Northern Ireland	1987–2007	8.7	25.8	34.5
Ford et al., 2007[12]	USA	1980–2000	8.5	24.2	32.7
Aspelund et al., 2010[13]	Iceland	1981–2006	0.5	32.0	32.5
Palmieri et al., 2010[14]	Italy	1980–2000	6.4	23.4	29.8
Hotchkiss et al., 2014[15]	Scotland	2000–2010	13.3	8.9	22.2
Bajekal et al., 2012[16]	England	2000–2007	13.9	5.5	19.4

CHD, coronary heart disease.

*Represents the attributable reduction in CHD mortality risk from changes in total cholesterol via statin treatment and other (e.g., diet related) causes.

resulting in lower LDL-C have demonstrated a greater impact on CV risk reduction (Fig. 1) than similar levels of statin-induced LDL-C reduction, presumably because statin treatment is typically initiated later in life.

For example, sequence variation in the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene was associated with a 15% reduction in LDL-C and a 47% reduction in CHD risk. Nonsense mutations of this gene were associated with a 28% reduction in LDL-C and an 88% reduction in CHD risk.[33] Naturally occurring, inactivating mutations of the Niemann-pick C1-like 1 (NPC1L1) gene in humans were associated with LDL-C reductions of 12 mg/dL and a 53% reduction in CHD risk.[29] A meta-analysis by Ference et al. demonstrated that 9 polymorphisms in 6 different genes were associated with a 54% reduction in CHD risk per 1 mmol/L reduction in LDL-C.[34] In comparison, only a 24% reduction in major coronary events with statin therapy over a median follow-up of 4.8 years has been demonstrated.[35] The significance of the chronicity of LDL-C exposure is also supported by recent epidemiologic analyses, which suggest that strategies for earlier initiation and prolonged LDL-C lowering might yield striking benefits for reducing CV risk.[36,37]

The association of LDL with CV risk is also supported by data from alternative measures of atherogenic lipoproteins. For example, at identical LDL-C levels, measurement of the number of circulating LDL particles has important prognostic value. A higher number of smaller LDL particles is associated with higher CV risk.[38] In one study of approximately 7000 participants without CV disease at baseline, LDL-attributable atherosclerotic risk was better indicated by LDL particle number when LDL-C and LDL particle number were discordant.[38] This may be due to the enhanced delivery of cholesterol to an atheroma by greater numbers of smaller LDL particles.[39] Furthermore, small dense LDL particles are more susceptible to oxidation and experience-decreased uptake by LDL receptors.[40]

Other laboratory markers of atherogenic lipoproteins correlate with LDL-C and also demonstrate similar relationships with CV risk. Both apolipoprotein (apo) B and non–high-density lipoprotein cholesterol (non-HDL-C) measure the contribution to atherogenic risk from the total number of atherogenic particles, including LDL, VLDL, IDL, chylomicrons, and lipoprotein(a).[19] The total number of apoB particles represents the total number of atherogenic lipoproteins, whereas non-HDL-C measures the total cholesterol content carried by these particles. These assays may be especially useful for patients with elevated triglycerides, who derive a greater proportion of their CV risk from triglyceride-rich particles than those with lower triglyceride levels. In a meta-analysis of epidemiologic studies of 3 atherogenic biomarkers, apoB was found to be the best CV risk predictor, followed by non-HDL-C and LDL-C.[41] In an analysis of statin-treated patients, non-HDL-C was found to be the best predictor of CV risk when compared to apoB and LDL-C.[42] These findings have led to the incorporation of non-HDL-C and apoB as primary or secondary treatment targets in recent guidelines. Although the roles of LDL particle number, apoB, non-HDL-C, or other measures such as the ratio of apoB/apoA1 for CV risk assessment are increasing, LDL-C remains the measure most commonly used for clinical trials and in clinical care.

Evidence-based strategies for LDL-C lowering

A number of approaches for LDL-C lowering have been well studied. These include lifestyle interventions, pharmacologic treatment, intestinal bypass surgery, and lipid apheresis. Below, we focus on the evidence for lifestyle interventions and pharmacologic treatment as well as their influence on cholesterol management guidelines.

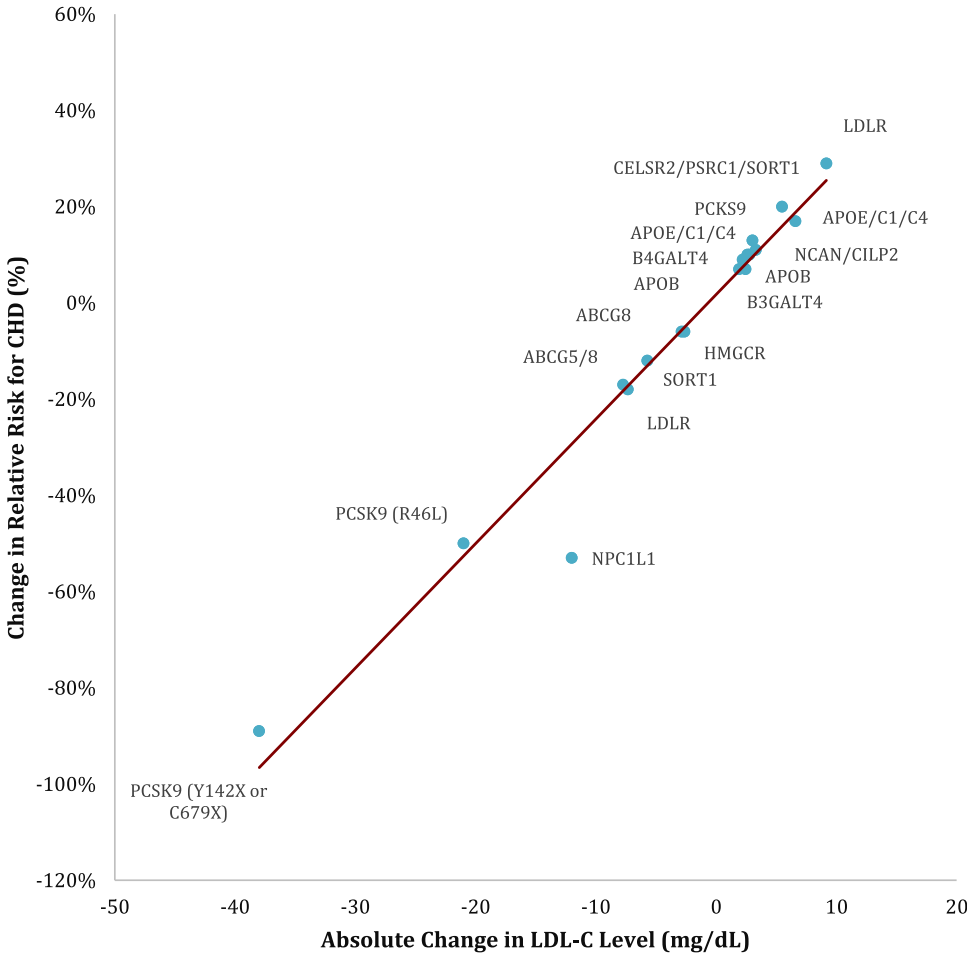

Figure 1 Association between absolute change in LDL-C levels over lifetime due to genetic variation and the change in relative risk for CHD.

Based on data from Willer et al., 2008,[27] Myocardial Infarction Genetics Consortium et al., 2014,[29] Linsel-Nitschke et al., 2008,[30] Cohen et al., 2006,[33] Ference et al., 2012,[34] and Stender et al., 2014[31] The figure has been limited to data from these studies regarding mutations with significant associations with both LDL-C levels and coronary outcomes. The studies were reviewed for duplicate reporting of data. Labels in the graph represent genes; repeated observations (e.g. LDLR) represent different SNPs. Where OR or HR were reported, change in relative risk was approximated as OR – 1 or HR – 1. The solid line represents estimated relationship via linear unweighted regression ($Y = 0.0259 \times X + 0.0173$).

CHD, coronary heart disease; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SNP, single-nucleotide polymorphism.

Lifestyle interventions

Societal changes, largely resulting from agricultural and industrial expansion, have led to higher population LDL-C levels. Evidence from hunter-gatherers has demonstrated that these populations have LDL-C levels typically ranging from 50 to 75 mg/dL. These populations are characterized by an absence of atherosclerosis, even in individuals living up to 8 decades. Furthermore, healthy, wild, adult primates have LDL levels of approximately 40 to 80 mg/dL.[43,44] In contrast, the currently accepted "normal" LDL-C range in Westernized societies is 100 to 160 mg/dL. This suggests that LDL-C levels in Western societies are grossly above the true physiologic range.[45]

Development and promotion of lifestyle recommendations to reduce CHD, initiated in the second half of the 20th century, have played a critical role in the decline of death from CHD.[7–16] One striking example began with a comprehensive, community pilot project conducted in North Karelia, Finland. In the late 1960s, men from this region had the highest CHD mortality rate in the world predominantly due to consumption of saturated fats and sodium, as well as smoking. Based on the results of the pilot project and implementation of its findings through national policy and health promotion initiatives (e.g., health education, development of a domestic vegetable oil industry) across Finland, a shift in the nationwide population distribution of cholesterol, blood pressure, and smoking was achieved. Reductions in saturated fat consumption led to a 60 mg/dL decline in mean national total cholesterol levels. Over the course of 35 years, in men aged 35 to 64 years, drastic reductions in

age-adjusted CHD mortality rates of 85% in North Karelia and 80% across Finland (down to 100 CHD deaths per 100,000 individuals) were achieved. Approximately 75% of this reduction was explained by a decrease in the 3 targeted risk factors. Among these, lowering of cholesterol accounted for most of the observed benefit.[46,47]

Cholesterol reduction can be achieved by a number of other changes in dietary habits. A meta-analysis of 67 controlled studies demonstrated that 2 to 10 g per day of dietary soluble fiber consumption reduces LDL-C by 2.2 mg/dL.[48] Phytosterol consumption reduces LDL-C by 13 mg/dL for every 2.15 g consumed daily.[49] Nut consumption (67 g daily) decreases LDL-C by 10.2 mg/dL and daily soy isoflavone consumption by 5 mg/dL.[50,51] Small LDL particle number has also been shown to be inversely correlated with crude-fiber consumption and positively related to dietary cholesterol intake, high-carbohydrate (and particularly high glycemic index) diets, and trans-fatty acid (TFA) consumption.[52,53] TFA consumption is associated with significantly higher LDL-C levels but has been decreasing over the past 3 decades due to efforts to eliminate industrial TFA in foods.[54]

Beyond individual foods, comprehensive diets such as the Mediterranean diet, which is comprised of primarily fruits, vegetables, legumes, grains, nuts, and olive oil, have been shown to reduce LDL-C by 10% after 5 weeks.[55] A recent study found that adults who followed the Mediterranean diet over 10 years were 47% less likely to develop heart disease compared to similar adults who did not follow this diet.[56] The more stringent Ornish diet has been shown to reduce LDL-C by 37%, although adherence is extremely difficult to achieve.[57]

Exercise training, independent of weight loss, does not significantly reduce LDL-C levels.[58–61] However, randomized studies indicate that physical activity results in a decrease in small LDL particle number.[62–64] Thus, a shift from higher numbers of smaller, more atherogenic particles to fewer, larger particles, may partially explain the reduction in CV risk associated with physical activity.[65]

Overall, an improved diet and exercise regimen most commonly lowers LDL-C by 10%–15%.[66] Consistent with genetic data demonstrating large CV risk reductions from chronic small to moderate reductions in LDL-C, improved dietary habits across the population beginning very early in life can yield large reductions in CHD and CHD-related healthcare spending. New research focusing on developing better dietary habits in children will be discussed later in the review.

Nonstatin pharmacologic therapies

In addition to lifestyle changes, LDL-C lowering has been advanced by drug-based therapy. The first pharmacologic treatment for LDL-C lowering, which demonstrated a significant reduction on a primary CV endpoint was cholestyramine, a bile acid sequestrant. In the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), cholestyramine lowered LDL-C levels by 12% (22 mg/dL) compared with placebo, with a relative reduction in the risk of nonfatal MI or CHD death by 19%.[67] The relative CV risk reduction per mg/dL reduction in LDL-C from this trial is consistent with the subsequent findings from the large meta-analysis of statin trials from the Cholesterol Treatment Trialists Collaboration (CTT).[35] No large, randomized trials have tested whether bile acid sequestrants would reduce CV events on top of statin therapy in a primary or secondary prevention population.

Before the statin era, niacin, which influences VLDL metabolism and lowers LDL-C, was compared to placebo in the Coronary Drug Project.[68] Although niacin did not reduce total mortality (primary endpoint), it did reduce nonfatal MI (secondary endpoint), which may be related to the 26 mg/dL (10.1%) reduction in total cholesterol. A post-trial exploratory analysis conducted 9 years after the completion of the trial found that these effects were associated with reduced mortality.

The role of niacin in patients well-treated with statins remains unclear. In the HPS2-THRIVE trial, the addition of extended-release niacin to a background of statin therapy reduced LDL-C and raised HDL-C levels by 10 mg/dL (15.6%) and 6 mg/dL (13.6%), respectively, compared to placebo. Niacin did not reduce the risk of major CV events and was accompanied by a range of serious adverse events.[69] The results of the much smaller AIM-HIGH trial also failed to demonstrate a CV benefit for niacin on top of statins.[70] A plausible explanation for the nonsignificant CV risk reduction findings in these trials is that niacin only resulted in a modest absolute reduction in LDL-C because the baseline LDL-C was well-controlled (e.g., $<$80 mg/dL). To date, it is unknown whether niacin results in a clinical benefit when added to statin therapy in patients with higher baseline LDL-C levels.

Ezetimibe inhibits the function of the NPC1L1 protein, which is responsible for transportation of dietary cholesterol from the gut lumen to intestinal enterocytes, thus reducing the absorption of dietary cholesterol.[71,72] Although ezetimibe was approved by the Food and Drug Administration (FDA) to lower LDL-C in 2002, its efficacy in reducing CV outcomes was only recently demonstrated. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) studied ezetimibe in a post-acute coronary syndrome (ACS) population with well-controlled LDL-C on background statin therapy. Ezetimibe resulted in a 15.8 mg/dL (23.9%) reduction in LDL-C levels and a 6.4% relative risk reduction in the primary composite endpoint of CV death, major coronary events, or nonfatal stroke at 7 years, as well as a 13% relative reduction in risk of any MI and 7.2% relative risk reduction in rate of major vascular events (MVE).[73] The findings from IMPROVE-IT suggest that the ezetimibe-induced CV risk reduction per mg/dL LDL-C reduction is similar to statins. Ezetimibe is the first LDL-C-lowering drug to demonstrate a reduction in CV outcomes in patients well-treated with statins.

Statin therapy

Statins inhibit the rate-limiting enzyme, HMG-CoA reductase, in the synthesis pathway of cholesterol. This results in lower intrahepatic cholesterol and an up-regulation of hepatic cell surface LDL receptors, resulting in enhanced receptor-mediated uptake of LDL and other apoB-containing lipoproteins from the circulation. Evidence supports their effectiveness in lowering coronary, cerebrovascular, and peripheral vascular events.

Primary prevention trials with statins have demonstrated a CV outcomes benefit in patients with hypercholesterolemia, diabetes mellitus, chronic kidney disease, and normal LDL-C (100 to 160 mg/dL) in the setting of other risk factors (Table 3).[74–82] A meta-analysis of the lowest risk subjects from statin trials found that 1 mmol/L (~39 mg/dL) of LDL-C reduction was associated with 38% and 31% decreases in the relative risk of MVE (nonfatal MI, coronary death, coronary revascularization, or stroke) in subgroups of 5-year predicted risk <5% and ≥5% to <10%, respectively. When these 2 subgroups were pooled, the absolute reduction in MVE was 11 per 1000 over 5 years.[35]

The benefit of statin therapy in reducing CV events in patients with known atherosclerotic CV disease has been well-established (Table 3).[83–93] In addition, more intensive (i.e., potent) statin regimens have been found to have greater efficacy compared to less-intensive regimens. The CTT meta-analysis demonstrated that 1 mmol/L (~39 mg/dL) reduction in LDL-C resulted in a 10% relative reduction in all-cause mortality and a 21% relative reduction in MVE for statins vs placebo. Decreases in the rate of individual endpoints per 1 mmol/L LDL-C reductions were major coronary events (24%), coronary revascularization (24%), ischemic stroke (20%), and any stroke (15%). Intensive statin (≥50% LDL-C lowering) vs less intensive (<50%) regimens further reduced LDL-C by 0.51 mmol/L (20 mg/dL) and led to another 15% relative risk reduction in MVE. These relationships were found to be consistent for all patient subtypes studied and indicated no threshold beyond which LDL-C lowering would not provide benefit (including <2 mmol/L [~80 mg/dL]), findings consistent with other large-scale studies.[6,94] The efficacy of statins on CV outcomes also appears to be consistent in both primary and secondary prevention populations across racial, ethnic, and regional practice differences.[35,94] In another CTT meta-analysis, statins were found to reduce LDL-C similarly in both men and women, with similar proportional reductions in MVEs. However, in the subgroup with no prior CV disease, the relative risk reduction in women was found to be lower compared with men (15% and 28%, respectively per 1 mmol/L LDL-C reduction).[95]

Statin adverse effects

Statins have also been evaluated for potential long-term adverse effects. Estimates of statin-related adverse events differ between randomized trials and observational studies, likely due to differences in patient selection. In randomized trials, elderly individuals, subjects with multiple comorbidities or on multiple medications, and women are generally excluded or under-enrolled despite being prescribed statins in clinical practice. Although observational trials have limitations, they provide useful data regarding adverse events in clinical practice.[96]

Statins have been reported to increase the incidence of nonserious musculoskeletal side effects (e.g., myalgia without elevation in creatine kinase) in uncontrolled observational studies (up to 20%), although this has not been detected in randomized, double-blinded, clinical trials.[96] Rhabdomyolysis occurs in an excess of 4 cases per 10,000 participants in intensive vs less-intensive statin trials, and only 1 case per 10,000 participants in less-intensive vs placebo trials.[94] Statin-induced transaminase elevation occurs at an excess rate of only 4.2 per 1000 patients and is reversible with dose reduction or discontinuation.[97] Past statin-related safety concerns including malignancy and cognitive dysfunction have been directly assessed using randomized trial data without any suggestion of a causal relationship.[98] Statin therapy is associated with a slight increase in risk of new onset diabetes. This relationship is dose-dependent, and in 1 meta-analysis, the risk of incident diabetes in participants receiving intensive statin treatment was 12% ($P > .05$) higher compared to moderate statin treatment.[99] However, the risk is low in absolute terms, and the CV benefits of statin therapy likely outweigh risk even in low-risk patients.[100,101]

Lipid-management guidelines

Guidelines offer practical recommendations for achieving consistent, evidence-based care. Guidelines for cholesterol management are available from the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS), American College of Cardiology (ACC)/American Heart Association (AHA), National Lipid Association (NLA), and International Atherosclerosis Society (IAS) among other committees.[17–20] These documents identify similar patient groups that benefit from LDL-C lowering. Below, we focus on the recommendations from the ESC/EAS and ACC/AHA, as this discussion illustrates the major differences between available guidelines.

ESC/EAS guidelines, 2011

The ESC/EAS joint guidelines recommend lifestyle modification as a component of all lipid-lowering treatment strategies. They also recommend consideration of an add-on pharmacologic treatment, with the intensity of therapy adjusted to achieve specific LDL-C goals.[18] Statin use is principally recommended, although the addition of bile acid sequestrants, cholesterol absorption inhibitors, or

Table 3 Summary of trials assessing the impact of statin therapy on LDL-C and cardiovascular outcomes

Study	Population	Drug (mg)	PEP*	Mean follow-up (y)	Baseline mean LDL (mg/dL)†	Change relative to comparator arm				
						LDL-C reduction (%)	LDL-C reduction (mg/dL)	Absolute CV risk reduction	Relative CV risk reduction	5-Year NNT‡
Primary prevention trials (statin vs placebo/usual care)										
WOSCOPS[74]	6595 men aged 45–64 y with high cholesterol and no history of MI in West of Scotland	Pravastatin 40	Nonfatal MI, CHD death	4.9	192	26%	49.9	2.4% ($P < .001$)	31% with pravastatin ($P < .001$)	41
AFCAPS/TexCAPS[75]	6605 patients without CHD and average LDL-C	Lovastatin 20–40	MI, UA, sudden cardiac death	5.2	150	25%	37.5	4.1% ($P < .001$)	37% with lovastatin ($P < .001$)	25
PROSPER[76]	5804 patients aged 70–82 y with preexisting vascular disease or risk factors	Pravastatin 40	Nonfatal MI, stroke, coronary death	3.2	146	34%	49.6	2.1% ($P = .014$)	15% with pravastatin ($P = .014$)	33
ALLHAT-LLT[77]	10,355 patients aged ≥55 y with high cholesterol, HTN, and ≥1 other CHD risk factors	Pravastatin 40	Nonfatal MI, CHD death	4.8	146	17%	24.8	1.1% ($P = .16$)	9% with pravastatin ($P = .16$)	88
ASCOT-LLA[78]	10,305 patients with HTN, ≥3 risk factors, and lower than average cholesterol	Atorvastatin 10	Nonfatal MI, CHD death	3.3 (median)	133	35%	46.4	3.4% ($P = .0005$)	36% with atorvastatin ($P = .0005$)	20
CARDS[79]	2838 patients with type 2 diabetes and without CV disease or high LDL-C	Atorvastatin 10	MI, UA with hospitalization, coronary revascularization, stroke, resuscitated cardiac arrest, CHD death	3.9 (median)	117	40%	46.8	3.2% ($P = .001$)	37% with atorvastatin ($P = .001$)	25
ASPEN[80]	2410 patients with type 2 diabetes and LDL-C below guideline targets	Atorvastatin 10	Nonfatal MI, UA with hospitalization, CABG, nonfatal stroke, resuscitated cardiac arrest, CV death	4.0 (median)	113	29%	32.8	1.3% ($P = .34$)	10% with atorvastatin ($P = .34$)	64

MEGA[81]	7832 patients with high cholesterol and without CV disease in Japan	Pravastatin 10–20	MI, angina, coronary revascularization, cardiac death	5.3	157	15%	23.2	1.7% ($P = .01$)	33% with pravastatin ($P = .01$)	62
JUPITER[82]	17,802 patients without CV disease, LDL-C <130 mg/dL and hsCRP >2 mg/L	Rosuvastatin 20	MI, UA with hospitalization, arterial revascularization, stroke, CV death	1.9 (median)	108 (median)	50%	54.0	0.59% ($P < .00001$)	44% with rosuvastatin ($P < .00001$)	66
Secondary prevention trials (statin vs placebo/usual care)										
4S[83]	4444 patients with CHD	Simvastatin 20–40	MI, resuscitated cardiac arrest, cardiac death	5.4 (median)	187	38%	71.1	9.0% ($P < .00001$)	34% with simvastatin ($P < .00001$)	12
CARE[84]	4159 patients with average LDL-C and history of MI	Pravastatin 40	Nonfatal MI, CHD death	5.0 (median)	139	32%	44.5	3.0% ($P = .003$)	24% with pravastatin ($P = .003$)	33
LIPID[85]	9014 patients with recent history of MI or hospitalization for UA	Pravastatin 40	CHD death	6.1	150 (median)	25%	37.5	1.9% ($P < .001$)	24% with pravastatin ($P < .001$)	63
LIPS[86]	1677 patients after first PCI with stable angina, UA, or silent ischemia	Fluvastatin 80	Nonfatal MI, coronary reintervention, cardiac death	3.9 (median)	131	27%	35.4	5.3% ($P = .01$)	22% with fluvastatin ($P = .01$)	16
HPS[87]	20,536 patients with CV disease, diabetes, or HTN in UK	Simvastatin 40	Nonfatal MI, coronary or non-coronary revascularization, stroke, CHD death	5.0	131	30%	38.7	5.4% ($P < .001$)	24% with simvastatin ($P < .0001$)	19
ALLIANCE[88]	2442 patients with CHD and hyperlipidemia	Atorvastatin 10–80	Nonfatal MI, UA with hospitalization, cardiac revascularization, resuscitated cardiac arrest, cardiac death	4.3	147	11%	16.2	3.5% ($P = .02$)	17% with atorvastatin ($P = .02$)	25
Secondary prevention trials (intensive vs less-intensive statin)										
PROVE-IT[89]	4162 patients recently hospitalized for ACS	Atorvastatin 80 vs pravastatin 40	MI, UA with hospitalization, coronary revascularization, stroke, all-cause death	2.0	124	29%	36.0	3.9% ($P = .005$)	16% with atorvastatin ($P = .005$)	15

(*continued on next page*)

Table 3 (*continued*)

Study	Population	Drug (mg)	PEP*	Mean follow-up (y)	Baseline mean LDL (mg/dL)†	Change relative to comparator arm				
						LDL-C reduction (%)	LDL-C reduction (mg/dL)	Absolute CV risk reduction	Relative CV risk reduction	5-Year NNT‡
A to Z[90]	4497 patients after ACS	Simvastatin 40 for 1 month then simvastatin 80 vs placebo for 1 month then simvastatin 20	Nonfatal MI, readmission for ACS, stroke, CV death	2.0 (median)	122	11%	13.4	2.3% ($P = .14$)	11% with simvastatin only ($P = .14$)	24
TNT[91]	10,001 patients with stable CHD	Atorvastatin 80 vs atorvastatin 10	Nonfatal MI, resuscitated cardiac arrest, stroke, CHD death	4.9 (median)	152	15%	22.8	2.2% ($P < .001$)	22% with atorvastatin 80 mg ($P < .001$)	45
IDEAL[92]	8888 patients with a history of MI	Atorvastatin 40–80 vs simvastatin 20–40	Nonfatal MI, resuscitated cardiac arrest, coronary death	4.8 (median)	157	16%	25.1	1.1% ($P = .07$)	11% with atorvastatin ($P = .07$)	88
SEARCH[93]	12,064 patients with history of MI	Simvastatin 80 vs simvastatin 20	MI, arterial revascularisation, stroke, coronary death	6.7	—	—	13.5	1.2% ($P = .10$)	6% with simvastatin 80 mg ($P = .10$)	106

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CHD, coronary heart disease; CV, cardiovascular; hsCRP, high-sensitivity C-reactive protein; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; PEP, primary endpoint; UA, unstable angina.

*In the ALLHAT-LLT, 4S, and HPS studies the primary endpoint (PEP) was defined as all-cause mortality. Only CV-related endpoints are summarized for these studies.

†Baseline LDL-C is intended to denote achieved LDL-C without statin therapy. In some cases, baseline LDL-C was back-estimated from available data.

‡5-year NNT estimated from available data on absolute risk reduction, relative risk reduction, and duration of follow-up.

niacin is suggested in patients unable to achieve the desired LDL-C goal despite statin monotherapy or in patients with statin intolerance. Use of the Systematic Coronary Risk Estimation (SCORE) model, validated in European populations, is recommended for the estimation of 10-year CV risk in populations without established atherosclerotic CV disease (ASCVD).[102] Established ASCVD (ACS, history of MI, stable angina, coronary or other arterial revascularization, stroke, transient ischemic attack or peripheral arterial disease presumed to be of atherosclerotic origin), diabetes, moderate/severe chronic kidney disease or a 10-year SCORE ≥10% establishes "very high risk" with an LDL-C goal of <70 mg/dL. "High risk" is established by marked elevation of a single risk factor (e.g., familial dyslipidemia or hypertension) or a 10-year SCORE ≥5 to <10% with an LDL-C goal of <100 mg/dL. Guidance on secondary targets (non-HDL-C or apoB) is also provided.

ACC/AHA guidelines, 2013

Like the ESC/EAS guidelines, the ACC/AHA guidelines recommend lifestyle modification as a component of all lipid-lowering treatment strategies. The ACC/AHA guidelines, however, recommend an alternative drug treatment approach and the new Pooled Cohort Equation for 10-year risk estimation in primary prevention cohorts. High-intensity statin therapy is recommended in (1) individuals 21 to 75 years of age with ASCVD; (2) individuals ≥21 years of age with LDL-C >190 mg/dL; and (3) individuals 40 to 75 years of age with no ASCVD but diabetes and LDL-C 70 to 189 mg/dL with ≥ 7.5% 10-year ASCVD risk. Moderate-intensity statin therapy is recommended in (1) individuals >75 years of age with ASCVD; (2) individuals 40 to 75 years of age with no ASCVD but diabetes and LDL-C 70 to 189 mg/dL with <7.5% 10-year ASCVD risk; and (3) individuals 40 to 75 years of age with no ASCVD or diabetes and LDL-C 70 to 189 mg/dL with ≥7.5% 10-year ASCVD risk.[17] These guidelines also suggest that when randomized control trial evidence demonstrates that nonstatin therapy further reduces adverse CV events when added to statin therapy, nonstatin therapy should be considered. A lipid profile is recommended after initiation of statin therapy, primarily to ensure adherence, but routine monitoring (e.g., every 6–12 months) is not recommended.

Comparison of ESC/EAS and ACC/AHA guidelines

The ACC/AHA's emphasis on a strategy of fixed-dose statin therapy based on risk without titration to pre-defined LDL-C goals is distinct from the ESC/EAS guidelines. The authors of the ACC/AHA guidelines decided on this approach to be consistent with the design of statin trials, which tested fixed dose (e.g., simvastatin 40 mg), rather than "titrate-to-goal" strategies. Simplification of the appropriate drug choice may result in greater treatment with potent statins, avoiding the well-documented problems of suboptimal statin dose initiation and limited uptitration.[103–105] A fixed dose strategy eliminates the need for routine lipid monitoring but raises the importance for thorough lifestyle and statin adherence evaluations and discussions at each clinical encounter. Rates of nonadherence are high, thus it is possible that without lipid monitoring, nonadherence may be less frequently identified.[106]

De-emphasis of achievement of specific LDL-C levels leaves it unclear whether physicians should consider the addition of other lipid-lowering treatments in patients with recalcitrantly high LDL-C despite high-intensity statin therapy. As discussed in previous sections, the body of evidence across genetic studies, epidemiologic studies, animal models, and post-hoc/meta-analyses of trial data indicate that residual CV risk is associated with achieved LDL-C. Reported after the publication of both guidelines, the IMPROVE-IT trial results demonstrated the effectiveness and outstanding tolerability of ezetimibe. These findings may shift the focus of future guidelines toward achievement of specific LDL-C goals (e.g., <50 mg/dL not just by statins but also ezetimibe).

A greater number of US patients are expected to qualify for statin therapy under the 2013 AHA/ACC guidelines (approximately 12.8 million more between the ages of 40 to 75 years) compared to the National Cholesterol Education Program Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults Adult Treatment Panel III (NCEP ATP III) guidelines.[107,108] The vast majority of this expansion in statin treatment would be based on a 10-year ASCVD risk ≥7.5%.[107,109] A recent analysis supports this expansion and suggests that treatment beyond this threshold (even down to ≥3.0% 10-year ASCVD risk) would be cost effective.[110]

Next steps in LDL-C-lowering therapeutics

Results from the IMPROVE-IT trial, taken together with the CTT meta-analysis of statin trials, demonstrate a continuous relationship between LDL-C lowering and CV risk reduction down to about 50 mg/dL.[73] Whether a beneficial net efficacy/safety profile can be achieved when targeting even lower LDL-C levels is unknown, but evidence suggests this may be a promising strategy for new drug development. In addition, there is a need for new LDL-C-lowering therapies for those on maximal statin therapy and/or ezetimibe who are unable to achieve current LDL-C goals (e.g., <70 mg/dL). These therapies may also be beneficial for patients not able or unwilling to take statins or other LDL-C-lowering drugs.

Targeting very low LDL-C

Post-hoc analyses of randomized trials consistently suggest a potential benefit from treatment to LDL-C levels beyond those currently recommended by guidelines. A

recent meta-analysis of statin trials indicated that individuals achieving LDL-C levels <50 mg/dL with statin therapy had a lower risk of major CV events, but possibly slightly higher risk of hemorrhagic stroke (although absolute event rate was low), compared to those achieving levels between 75 and <100 mg/dL.[111] One trial included in the meta-analysis (JUPITER), reported no systemic increase in adverse events in those achieving LDL-C <50 mg/dL (median follow-up of 2 years).[112] In the PROVE IT-TIMI 22 trial, achieving LDL-C ≤40 mg/dL on atorvastatin 80 mg was associated with a lower risk of major CV events without any increase in adverse events (mean follow-up of 2 years).[113] Another analysis of JUPITER demonstrated that achieving LDL-C <30 mg/dL was also not associated with a higher total adverse event rate; it was, however, associated with more physician-reported diabetes, hematuria, hepatobiliary disorders, and insomnia.[114]

Naturally occurring examples in humans suggest that good health may coexist with prolonged exposure to very low LDL-C levels. Umbilical-cord measurements suggest that fetal growth and development occurs in the setting of LDL-C <40 mg/dL.[115,116] In individuals with hypobetalipoproteinemia, lifelong very low levels of LDL-C (<15 mg/dL) has not been associated with adverse effects.[117] In a report of 2 individuals, both women with homozygous loss-of-function PCSK9 mutations resulting in LDL-C ≤15 mg/dL, subjects appeared to be asymptomatic with normal development, intelligence, and ability to bear healthy children.[118,119] Thus, it is possible that the physiologic range for LDL-C extends to these extremely low levels. These data provide reassurance for an acceptable safety profile to pursue research in novel LDL-C lowering mechanisms to be used in conjunction with potent statins or potent statins plus ezetimibe.

Novel therapeutic agents

Studies of genetic mutations associated with potentially beneficial lipid profiles, including lower LDL-C, have led to the identification of targets for the development of novel therapeutic agents.[120] An example is the PCSK9 inhibitors, alirocumab, evolocumab, and bococizumab. Circulating PCSK9 increases endosomal and lysosomal degradation of hepatic LDL receptors resulting in the decreased ability to clear LDL particles from the circulation.[121] PCSK9 inhibitor-based therapies are fully human monoclonal antibodies that bind to circulating PCSK9 resulting in greater numbers of hepatic LDL receptors.

Alirocumab has been assessed recently in phase III trials with 75 mg and 150 mg Q2W dosing.[122] The recent ODYSSEY LONG TERM study investigated alirocumab's efficacy and safety in 2341 patients. In high CV risk patients on statins, alirocumab compared with placebo resulted in a 62% reduction in LDL-C and the incidence of major CV events by 48% ($P = .02$) in a post-hoc analysis with 78-week follow-up.[123] The ongoing ODYSSEY OUTCOMES study in approximately 18,000 post-ACS patients is assessing the impact of adding alirocumab to statin therapy on major CV events.[124]

Evolocumab has also recently been evaluated in phase III trials with 140 mg every 2 weeks (Q2W) and 420 mg every 4 weeks dosing.[122] The recent OSLER I and II studies assessing efficacy and safety in 4465 patients demonstrated that evolocumab plus standard therapy reduced LDL-C by 61% and the incidence of major CV events by 53% ($P = .003$) compared to standard therapy alone in a prespecified but exploratory analysis with 1 year follow-up.[125] The ongoing FOURIER study in approximately 27,500 patients with established CV disease on statin therapy is assessing as its primary endpoint whether addition of evolocumab reduces the incidence of major CV events.[126]

In the OSLER and ODYSSEY LONG TERM studies, the rate of any adverse events and/or serious adverse events was similar in patients receiving PCSK9 inhibitors compared to placebo. The rate of neurocognitive events was higher in PCSK9 inhibitor groups, although the total number of events was low.[123,125] Rates of newly diagnosed diabetes and worsening of preexisting diabetes were similar.[123] A meta-analysis of 24 randomized control trials demonstrated similar rates of serious adverse events between patients receiving PCSK9 inhibitors compared to those who did not (9.26% vs 7.73%, $P = .88$).[127] Data from the ODYSSEY LONG TERM study revealed that driving LDL-C levels to <25 mg/dL did not increase adverse events compared to placebo.[123]

In light of their efficacy and favorable safety profile, both alirocumab and evolocumab have been approved by the FDA for use in patients with clinical ASCVD who require additional LDL-C lowering, and in adult patients with heterozygous familial hypercholesterolemia already on maximally tolerated statin therapy.

Another novel pharmacologic approach for LDL-C lowering is CETP inhibition. CETP shuttles triglycerides and cholesteryl esters between apoB-containing lipoproteins and HDL, causing remodeling of circulating lipoproteins. Potent inhibition of this enzyme dramatically increases HDL-C and can reduce LDL-C and lipoprotein(a). The failure of the early CETP inhibitors, torcetrapib (due to an increased risk of CV death presumably secondary to off-target effects), dalcetrapib (presumably due to minimal reductions in LDL-C), and most recently evacetrapib (Phase III trial stopped early due to low probability of achieving the primary endpoint) have not fully closed the door on CETP as a drug target.[128–131] The CETP inhibitor, anacetrapib, has been shown to increase HDL-C by 140% and decrease LDL-C by approximately 40% on top of statin therapy, and is currently undergoing evaluation in the REVEAL HPS3-TIMI 55 trial.[132] Although anacetrapib reduces LDL-C, it does increase small (and potentially more atherogenic) LDL particles.[133]

Table 4 Novel LDL-C lowering therapies and their respective CV outcomes trials

Drug type	Trial name	Study population	Planned enrollment	Estimated completion
PCSK9 inhibitors				
Evolocumab	FOURIER	Established CV disease	27,500	February, 2018
Alirocumab	ODYSSEY OUTCOMES	Recent ACS	18,600	February, 2018
Bococizumab	SPIRE I	High risk for CV events	17,000	June, 2018
Bococizumab	SPIRE II	High risk for CV events	9,000	March, 2018
CETP inhibitor				
Anacetrapib	REVEAL	Established CV disease	30,600	January, 2017

ACS, acute coronary syndromes; CETP, cholesterol ester transfer protein; CV, cardiovascular; PCSK9, proprotein convertase subtilisin/kexin type 9.
Source: clinicaltrials.gov.

LDL-C lowering through these therapeutic agents offers a novel strategy to reduce residual risk of atherosclerotic CV events, especially after recent failures of treatments aimed at other targets, including HDL-C and lipoprotein-associated phospholipase A_2.[134] Data from CV outcomes trials of novel, potent LDL-C lowering drugs will provide insight into the net balance of benefits, and risks associated with even greater LDL-C reduction and lower levels of achieved LDL-C (Table 4).

Population-level and health-system initiatives

Population-level and health-system changes could have an immense influence on improving lifestyle behaviors, cholesterol screening, and access to providers and evidence-based therapies. As previously discussed, the Finnish experience is just one example of an effective population intervention guiding public health policy but illustrates the profound population effect (i.e., mean total cholesterol reduction 60 mg/dL) local and national policies can achieve.

Lifestyle initiatives

Long-term improvements in diet and exercise through behavioral interventions may significantly reduce LDL-C, which, when initiated in children and adolescents, might result in dramatic reductions in the incidence of CV events later in life. In Bogota, Colombia, a preschool-based intervention targeting 1200 children improved knowledge, attitudes, and habits related to healthy eating and physical activity at 1 year. Three years later, further improvements were seen in the same endpoints in this cohort.[135] This suggests that interventions targeting periods of behavioral malleability (e.g., ages 3 to 5 years) can have beneficial, sustained impacts on lifestyle habits.

Disease awareness

Lack of awareness is a significant barrier to the appropriate treatment of hypercholesterolemia. The Minnesota Heart Survey demonstrated that from 2000–2002 over half of men and women at or above moderate risk of CHD were unaware of their elevated cholesterol.[136] Data from National Health and Nutrition Examination Survey during 1999–2002 revealed that only 63% of US adults had their cholesterol screened within 5 years (as recommended by the NCEP guidelines).[137] Furthermore, data from both studies demonstrated that a high proportion of individuals who were aware of their elevated cholesterol levels were not receiving treatment. Policy efforts must focus on better screening with appropriate triage to medical providers for at risk patients. The Affordable Care Act not only expands health insurance coverage, but also promotes preventative screening, including for lipid disorders.

Medication adherence

Medication nonadherence compromises the effectiveness of proven therapies. Registry data of post-MI patients from a large panel of US hospitals from 2003–2009 indicate that approximately only one-third of patients were discharged with an intensive statin.[138] Recent data of those insured under a large commercial plan showed that just 49% of post-MI patients were adherent to statins at 1-year follow-up.[139] In England in 2007, the rate at which statin prescriptions were filled for patients with established CV disease was somewhat higher at 66%–85%.[16]

Causes of statin underutilization are likely multifactorial. A number of patient factors have been associated with statin adherence.[106] Age predicts nonadherence in a bimodal fashion, with the oldest (>70) and youngest (<50) being the poorest adherers.[140,141] Patients that are non-Caucasian, low-income, female, or smoke are less likely to be compliant with lipid-lowering drugs, although these demographics are not always reliable predictors.[142,143] Patients with a history of CHD are up to 3 times more likely to be adherent than those without a history of CHD.[144,145] Limited income, polypharmacy, dementia, and depression and/or anxiety have all been shown to increase nonadherence.[146,147] Health system–related issues also influence adherence. Medicaid patients are approximately 43% less likely to have high statin

persistence, supporting that individuals or families with low incomes and limited resources may be prone to nonadherence.[148] High insurance copayments also diminish statin adherence.[149] Medication expense is also an important factor. In the USAGE study, cost prompted nearly half of patients to switch statins.[150]

Patient adherence can be improved by interventions that focus on extended care with nonphysician providers, better follow-up, and increased contact with physicians.[151] Enhancing the physician-patient communication axis and providing counseling can improve statin adherence.[152] Practical interventions such as medication reminders and improved patient education are also effective.[153] The use of combination "polypills" may also help simplify complex medication regimens.[154]

Provider behavior also contributes to suboptimal statin use. Evidence suggests that providers often fail to start and uptitrate statins appropriately.[103–105,138] This may be secondary to reluctance to re-evaluate long-standing treatments, mislabeling patients as "statin intolerant" or "allergic", and busy workflows that interfere with the required time and attention necessary to review and optimize medication regimens. As previously suggested, providers may not provide effective education on statin indications, proper dosing, tolerability, and safety.[103,105,138] In addition, providers may underestimate the success rate of statin rechallenges. In an observational study of clinical practices from a single academic institution over 9 years, 17% of 107,835 patients discontinued statin use due to events labeled as "statin related". Of patients who discontinued statins and were rechallenged over the subsequent 12 months, greater than 90% eventually tolerated statin use.[155]

Technological solutions

Health system barriers can propagate gaps in chronic disease care. New payment models that reward coordination and quality are being used by the Center for Medicare and Medicaid Services. These models depend on electronic health records (EHRs) to provide the tools necessary to track and improve quality of care. EHR adoption and use for a broader array of tasks is incentivized by the meaningful use criteria established by the HITECH Act. Studies already have demonstrated the impact of EHR-based performance feedback coupled with a quality improvement tool for LDL-C reduction. For example, use of EHRs at Kaiser Permanente was associated with statistically significant improvements in treatment intensification as well as downstream LDL-C reductions.[156] This was attributed to greater alignment with quality measures and clinical guidelines as well as increased availability of information and decision support through the EHR. Other technological interventions such as telemedicine have been shown to improve outcomes in chronic conditions (i.e., diabetes) and are currently undergoing evaluation for dyslipidemia.[157] EHRs and other technological initiatives have the potential to support provider decision-making, patient self-management, and quality improvement.[158]

Overall, hypercholesterolemia is best treated through a multi-faceted strategy similar to other public health issues, such as tobacco use. LDL-C reduction will be best achieved not only by continued drug development, but by comprehensive public health initiatives (e.g., nutritional content reporting in restaurants, food product labeling), cholesterol screening, promotion of healthy lifestyles, and technological and health system advances that facilitate and promote value-based care.

Conclusion

CV disease causes significant worldwide morbidity and mortality and contributes to substantial health care spending. The treatment of hypercholesterolemia, and specifically elevated LDL-C, represents an established strategy to diminish incident CV events and mortality. Numerous studies have established the continuous, graded, benefit conferred by LDL-C reduction on CV event risk and mortality. Future studies should focus on the impact and safety of targeting "very-low" LDL-C, earlier initiation of LDL-C–lowering interventions, the development and impact of novel therapeutic agents, as well as the use of evidence-based policy and regulatory initiatives to reduce environmental causes of elevated LDL-C on a population level.

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