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Lipid Lowering Therapy in Primary Prevention: Where Are We?

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Abstract

Purpose of Review: Apart from lifestyle modifications, lipid lowering strategies have become the cornerstone in primary prevention of atherosclerotic cardiovascular disease (ASCVD). Although multiple primary prevention guidelines are available, a significant gap exists between evidence-based guidelines and day-to-day practice. Not only adherence to guideline-based treatment but achieving guideline-directed statin intensity are still suboptimal. Based on recent data, cardiovascular outcome benefits are still observed with profound lowering of low density lipoprotein cholesterol (LDL-C), to levels lower than current guideline goals. With better understanding of signaling molecules, genetics and development of advanced tools, lipid lowering strategies have focused more on biological, RNA-, and gene-related approaches.

Recent Findings: Over the last decade, lipid lowering strategies have shifted from targeting HMG-CoA reductase to focusing on the proprotein convertase subtilisin/kexin type 9 (PCSK9) protein. By binding with low density lipoprotein receptors (LDL-R) on hepatocytes, the PCSK9 protein blocks the recirculation of the LDL-R and plays an integral role in LDL-C clearance. Data from recent PCSK9 trials show that profound reduction of LDL-C could be achieved with PCSK9 monoclonal antibodies and there is no lower limit of LDL-C below which it does not show cardiovascular risk benefits. Currently, preliminary phase III trials are assessing the safety and efficacy of PCSK9 vaccines with purpose of inducing autoantibody production to neutralize the PCSK9 protein. Phase III trials of small interfering RNA, which interrupts the production of PCSK9 protein, are also ongoing. In addition, a recent PCSK9 gene editing study in primates has shown sustained reduction in LDL-C.

Summary: Since ASCVD is a life-long vascular remodeling process, early initiation and aggressive lowering of LDL-C is imperative to achieve sustained benefits in cardiovascular outcomes. Novel lipid lowering therapies targeting the PCSK9 protein, including its neutralization by monoclonal antibodies, halting its production, or targeting the PCSK9 gene itself, are promising lipid management strategies which could prevent and potentially eradicate ASCVD.

Keywords: primary prevention, cardiovascular disease, statin, PCSK9, lipid lowering strategy.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is a progressive life-long disease that may lead to cardiovascular (CV) events such as myocardial infarction (MI), ischemic stroke, or peripheral artery disease (PAD). Despite tremendous progress in research and treatment, ASCVD remains the leading cause of death not only in the United States but in different parts of the world.[1,2] The World Health Organization estimates that 32% of mortality worldwide is due to ASCVD, and 85% of premature ASCVD is preventable with aggressive risk factor modification and lifestyle changes.[3,4] Prior evidence clearly indicates that the successful reduction of ASCVD depends not only on lifestyle modification, but also to a greater degree on interventions to reduce the lifelong exposure to highly atherogenic lipid particles,[5,6] which have become the targets of current and future lipid lowering strategies.

Substrates for Development of ASCVD

It has been well established that the low-density lipoprotein cholesterol (LDL-C),[7] apolipoprotein B (Apo-B)[8] and lipoprotein a [(Lp(a)][9] are the major atherogenic substrates for the development of ASCVD. As shown by Ference et al., large scale meta-analyses of Mendelian randomized studies, prospective cohort studies, and randomized controlled trials clearly established a direct relationship between LCL-C and ASCVD.[7] Risk of CVD mortality and non-fatal MI can be reduced by 20-25% just by reducing the LDL-C by 1 mmol/L.[5]

ASCVD risk is reflected by the total number of atherogenic particles, not by the cholesterol content.

One molecule of Apo-B is attached to each of the atherogenic lipid particles: LDL-C, Lp(a), intermediate density lipoprotein, and very low-density lipoprotein. Therefore, measuring the serum concentration of Apo-B provides a better estimate of the total atherogenicity of the lipid profile. As shown by Pencina et al. in the Framingham Offspring Study, Apo-B $\geq$ 100 confers higher CVD risk independent of the LDL-C level.[8]

Erqou et al. in 2009 demonstrated that increased Lp(a) is associated with increased risk of MI, ischemic stroke, aortic stenosis, and mortality.[9] ASCVD risk increases with Lp(a) level > 30 mg/dL, is substantially higher at levels > 50 mg/dL, and has the worst prognosis, similar to heterozygous familial hypercholesterolemia with Lp(a) level > 180 mg/dL.[9]

The absolute risk of major adverse cardiovascular events has been shown to have a proportional relationship to the concentration of Lp(a).[10] Recent meta-analyses of prospective, population-based studies show that increased Lp(a) is associated with higher risk of ASCVD, and this relationship is independent of the level of other lipoproteins, including LDL-C.[11] Unless specifically treated, Lp(a) concentration is not influenced by age, sex, lifestyle factors, and is regulated by a single gene locus LPA.[11] Recently, Trinder et al. demonstrated that Lp(a) concentration does not change much over time, and a single measurement of Lp(a) molar concentration is a good low cost screening tool for CV risk assessment and can redefine risk in individuals with family history of premature CAD.[12]

Shortcomings of Current Prediction Modeling and Guideline Recommendations for Primary Prevention

To identify asymptomatic individuals at risk for future CV events, several predictive models have been developed, such as the Framingham Score Model,[13] Pooled Cohort Equations (PCE),[14,15] Systemic Coronary Risk Estimation 2 (SCORE2),[16] and Systemic Coronary Risk Estimation 2-Older Persons (SCORE2-OP).[17]

The use of statins in primary prevention of ASCVD has been well established[14,18,19] and is recommended for specific risk groups by major prevention guidelines internationally: 2019 American College of Cardiology/American Heart Association (ACC/AHA) guideline,[15] 2021 European Society of Cardiology (ESC) guideline,[20] Canadian guideline,[21] and Chinese guideline.[22] The 2019 ACC/AHA guidelines on primary prevention recommend starting statin therapy in high- and specific intermediate-risk groups as shown in **Table 1**, and additional risk-enhancing factors were added to further redefine risks in borderline and intermediate risk groups[15] and it is known that PCE-based risk scoring can both under- and over-estimate CVD risk.[23-27]. Despite being widely used, the current risk assessment models do not have precise diagnostic accuracy in predicting high-risk individuals who are going to have their first CV event.[25,28] Coronary calcium score (CACS) has also become an important tool and is incorporated in the 2019 ACC/AHA primary prevention guidelines to redefine ASCVD risk to accurately identify those individuals at both high- and low-risk for a CV event.[15]

Table 1. Recommendation for Statin Therapy According to 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease.

Any Age		LDL ≥ 190 mg/dL (≥4.9 mmol/L)	Lifestyle modification High-intensity statin (LDL-C reduction ≥50%)
Age 0 – 19 years		Familial Hypercholesterolemia	Lifestyle modification Statin
Age 20 – 39 years		Family history of premature ASCVD and LDL ≥160 mg/dL (≥4.1 mmol/L)	Lifestyle modification Statin
Age 40 – 75 years	Diabetes		Lifestyle modification Moderate-intensity statin (LDL-C reduction 30-<50%) Risk-assessment to consider high-intensity statin
Without Diabetes -> 10 -year ASCVD risk assessment			
Age 40-75 years	< 5% (Low Risk)		Lifestyle modification
	5% - <7.5% (Borderline Risk)		Lifestyle modification
		If ASCVD risk enhancers are present	Lifestyle modification Moderate-intensity statin (LDL-C reduction 30-<50%)
	≥7.5% - <20% (Intermediate Risk)	If ASCVD risk enhancers are present	Lifestyle modification Moderate-intensity statin (LDL-C reduction 30-<50%)
	≥20% (High Risk)		Lifestyle modification High-intensity statin to reduce LDL-C ≥ 50%.

ASCVD Risk Enhancers

- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- History of preeclampsia, premature menopause in women
- Inflammatory disease (such as, rheumatoid arthritis, psoriasis, Human immune deficiency virus)
- Ethnicity (e.g., South Asian)

Lipid/Biomarkers

- Persistently elevated triglycerides (≥175 mg/dL (≥2.0 mmol/L)
- High sensitivity C-reactive protein ≥ 2.0 mg/L
- Lipoprotein (a) levels ≥ 50 mg/dL (≥125 nmol/L)
- apoB ≥ 130 mg/dL
- Ankle-brachial index (ABI) < 0.9

Adapted from 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease.[15]

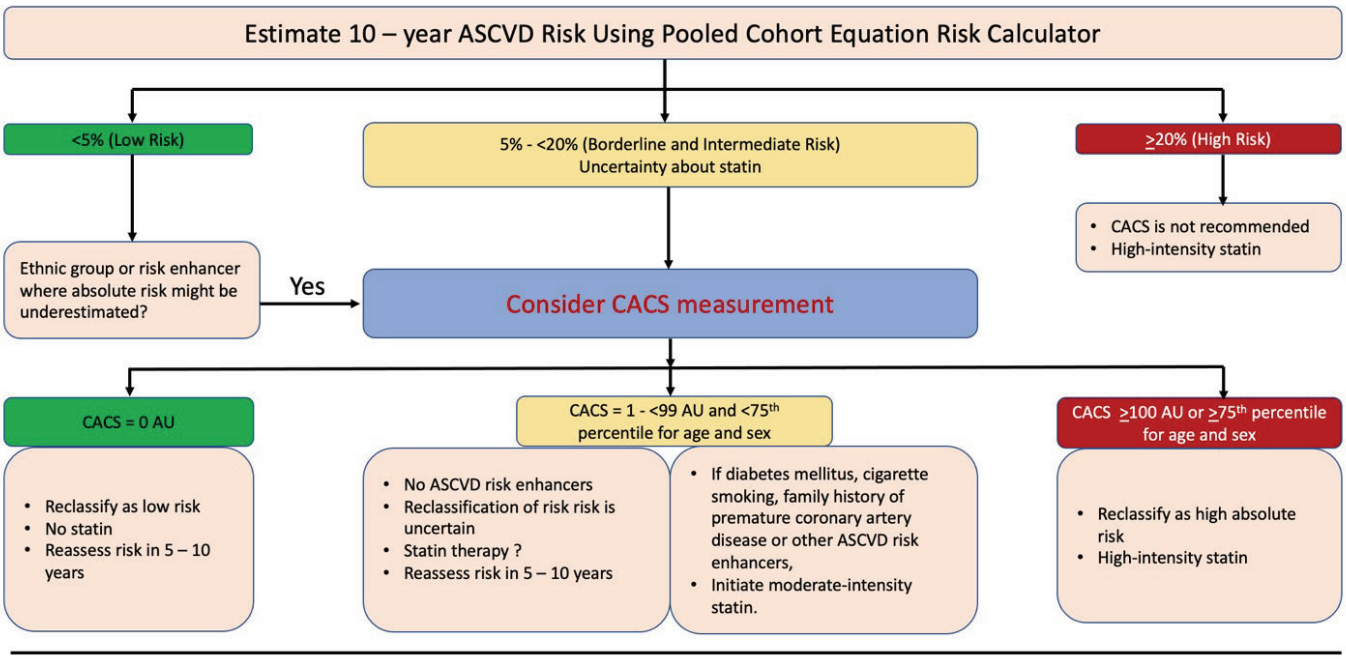
Role of Coronary Artery Calcium Score (CACS) in Redefining CV Risk

Recent review of multiple studies over the last 30 years by Drs. Khurram Nasir and Miguel Cainzos-Achirica has shown a clear relationship between elevated CACS and ASCVD events.[29] CAC registry data also showed that patients with CACS > 0 AU benefitted with statin therapy with significant reduction in CV events compared to no statin.[30] Data from a recent Australian study[31] of 1000 asymptomatic individuals with strong family history of premature CAD showed that of the individuals initially classified at low risk, 77% had a CACS above 100 AU, and 19% of subjects initially thought to be at moderate risk had a CACS of 0. There is growing evidence that the quantification of CACS can redefine risk assessment to identify individuals who could benefit from intensity-appropriate statin therapy. On the other hand, a zero CACS can redefine an individual's CV risk to the low end and can help reduce patient's concerns, particularly in those who are reluctant or unable to tolerate a statin if otherwise indicated by initial risk assessment. As incorporated in newer guidelines, the quantification of CACS appeared to be the best predictor of ASCVD events in the intermediate risk group over a 10-year period.[15] A recently published randomized controlled trial comparing a CACS-versus PCE risk score-based strategy also validated the concept that CACS-guided strategy is more cost-effective, could be individualized, and is helpful in motivating patients to start and adhere to long-term statin therapy.[32]

Utilization of CACS

Based on 2019 ACC/AHA primary prevention guidelines[15] and the National Heart Foundation of Australia position statement,[33] an approach to CAC scoring is depicted in **Figure 1**. First, a 10-year ASCVD risk is calculated using either the PCE[15] or ESC SCORE2[16] risk calculator. CACS is not recommended for patients who are already defined as high absolute CV risk.[34,35] In moderate-risk patients when initial risk status is close to high-risk, CACS is helpful to decide the intensity of the statin therapy. A CACS of 0 AU can redefine a moderate risk individual to low-risk status. However, it does not rule out non-calcified plaque. Patients with a history of smoking, diabetes, and family history of premature coronary artery disease may have non-calcified plaque, and the CV risk should not be underestimated even if CACS is zero.[15,36,37] Patients with CACS 1-99 AU and <75th percentile, if risk enhancers are present, should qualify for moderate-intensity statin therapy. CACS of > 99 AU or ≥75th percentile categorizes the patient to high absolute risk. Repeat CACS is not necessary in this group, and patients should follow risk management strategies according to guidelines.

Figure 1. Coronary Artery Calcium Score (CACS) in Primary Prevention of ASCVD



Adapted from 2019 ACC/AHA guideline[15] and National Heart Foundation of Australia Position Statement.[33]

Coronary Computed Tomography Angiography and Detection of Early Atherosclerosis

The new generation of coronary computed tomography angiography (CCTA) scanners with higher resolution and low radiation exposures are gaining more attention since they can evaluate not only the extent of calcified and non-calcified plaque burden but also can characterize the composition of atherosclerotic plaques.[38] Low attenuation plaque is associated with future CV risk and could be mitigated with statin therapy or other preventive measures.[39] On the other hand, coronary artery calcification reflects more advanced atherosclerotic plaque. Though plaque burden itself might regress with aggressive lipid lowering therapy, calcification does not decrease but rather increases with statin therapy.[40] When CACS is already above 99 AU, repeating CACS does not add any further incremental value. Recently, a strong association of subclinical atherosclerosis and gene score has been shown in a cohort study of young adults by Natarjan et al.[41] In younger patients with strong family history of premature CAD or with familial hypercholesterolemia, CCTA may be helpful to identify patients for whom aggressive intervention with lipid-lowering therapy along with lifestyle modification should be initiated.

How Early the Treatment and How Low the LDL-C?

Different studies have shown that aggressive risk factor management and treatment of cholesterol can stabilize and to some degree, regress atherosclerotic plaque.[42,43] The FOURIER trial[44] showed that even LDL-C levels as low as 10 mg/dL showed CV benefits. The ODYSSEY-OUTCOMES trial[45] also showed all-cause mortality benefit with LDL-C levels as low as 30 mg/dL. Data from these PCSK9 inhibitor trials clearly show that in high-risk groups, profound reduction in LDL-C levels substantially reduces the risk of CV events and there is no lower limit of LDL-C below which CV benefit is not shown. However, some residual risk of acute CV events persists even when LDL levels are greatly reduced.[44,46,47]. Despite possible regression of atherosclerotic plaque with aggressive lipid lowering, the necrotic core still exists, reflecting the residual CV risk. It is well known that the atherosclerotic process starts early in adulthood as fatty streaks.[48-50] In animal models, lowering LDL-C levels below 25 mg/dL could completely regress fatty streaks and normalize endothelial cell function.[51] Based on the cumulative data, intervening on these early lesions is gaining attraction with the goal to achieve complete resolution of the atherosclerotic process.[52-55] It is becoming clearer that in primary prevention, apart from healthy diet, exercise and lifestyle changes, the focus should be on slowing the progression of the atherosclerotic disease process as early as possible to prevent future CV events.[56]

With that hypothesis in mind, the Eliminate Coronary Artery Disease (ECAD) trial[57] was launched in 2014 and included younger age groups (35-50 years for men and 45-59 years for women) with at least one risk factor, such as smoking, hypertension, obesity, family history of CAD, and South Asian ancestry, with follow-up over a 10-year period. The trial was designed to validate the concept that treating early and keeping the LDL-C low could not only abort the atherosclerotic plaque formation but also halt the progression of the existing disease. Similarly, the proposed CURE ATHERO trial[58] by Robinson et al., included even younger age groups (25 - 55 years) with target LDL-C goal of 20 - 40 mg/dL and hypothesized that the clinical burden of atherosclerosis might be eliminated at its early stages by aggressively lowering the LDL-C. Recent data suggest that lower LDL-C, earlier treatment, and sustained reduction of the LDL-C are important to achieve a meaningful CV risk benefit. Naturally, the following questions arise: what are the cost and side-effects profile with long-term use of lipid-lowering agents?

Statin Side Effects

A recent systematic review of 62 randomized controlled trials revealed that statins did not significantly increase the incidence of muscle disorder or diabetes, though they were associated with self-reported muscle symptoms.[59] This analysis also showed that statin-induced adverse effects were not associated with the type of statin and dose, except for atorvastatin for which a dose-dependent effect on liver dysfunction was noted.[59] In recent PCSK9 trials in which the achieved LDL-C levels were very low, no significant difference was noted in the treated versus control groups with regard to potential side effects,

such as new-onset diabetes, hemorrhagic stroke, or new onset dementia.[60-65] As reported by Cai et al., the incidence of clinically relevant muscle symptoms in statin treated patients was not significantly different compared to that of the control group, suggesting that reported muscle symptoms with statins may be, at least in part, attributable to patients' perception or the so-called "nocebo" effect.[59] The investigators on behalf of the Lipid and Blood Pressure Meta-Analysis Collaboration and the International Lipid Expert Panel recently published a large meta-analysis including 176 studies (112 randomized controlled trials and 64 cohort studies) worldwide which showed that the prevalence of statin intolerance was low (9.1%) and even lower (5.9%) when using European Society of Atherosclerosis criteria.[66] Physicians should carefully evaluate patients' symptoms to see whether they are truly related to statins or rather patients' perception. Proactive, continuing physician-patient discussion is essential to ensure patients are not unnecessarily and preemptively taken off of treatment proven to reduce CV risk.

Statins in Elderly

Though benefits of statins in patients 75 years or older are well established for the secondary prevention of ASCVD events and CV mortality,[67-70] the Lipid-Lowering Trial component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) showed no benefit of pravastatin in primary prevention in individuals aged 75 years or older.[71] In a large cohort study from the Catalan Database in Spain, Ramos et al. showed that among participants above age 74 years without type 2 diabetes, statin treatment did not reduce ASCVD events or all-cause mortality.[72] Patients with type 2 diabetes in this subgroup, however, had significant reduction in ASCVD events and all-cause mortality and this beneficial effect was markedly diminished with age above 85 years.[72] Current ACC/AHA guidelines recommend assessment of risk status in patients 75 years or older and encourage physician-patient discussion to decide whether to continue or initiate statin treatment.[15]

Gap between Guidelines and Lipid Control

A recent ESC EURObservational Research Program EUROASPIRE V survey in 16 European countries showed that in the primary care setting, at least 35% of patients with high ASCVD risk failed to achieve adequate lifestyle, blood pressure, lipid, and glycemic controls as defined by recent guidelines on primary prevention of CVD,[73] A significant gap exists between evidenced-based guidelines and day-to-day clinical practice as demonstrated by multiple other surveys in the US, Europe, and other parts of the world.[74-78] Statin therapy is highly cost-effective,[79] and the number needed to treat is only 10 to prevent 1 ASCVD event.[80] Despite the efficacy of statins and emphasis in guidelines, a recent large scale primary prevention study in the US by Saeed et al. showed that 30% of high-risk and 41% of intermediate-risk group individuals who required statin therapy according to guidelines never received the treatment over a 6 year follow up period and among those who did receive statin, it took up to 2 years to achieve the guideline-directed statin intensity.[81] Similar data from a recent Veterans Affairs primary prevention cohort study showed that about one-third of statin eligible patients did not receive any statin prescription over a 10-year follow up period.[82] In practice, multiple issues with statin therapy are well-identified: 1) lack of effective provider-patient discussion; 2) suboptimal adherence to guideline-based treatment and also achieving guideline-directed statin intensity; 3) patient's concerns about statin side effects and reluctance to continue long-term treatment; 4) lack of adequate follow up, particularly in low- and middle-income countries; and 5) patients' lack of adherence to medication. As evidenced by data from multiple large cohort studies, physician-patient interaction should be more proactive to address these areas to achieve a sustained meaningful impact on CV risk reduction.

Novel Lipid Lowering Strategies

Over the last several decades, multiple randomized controlled trials have shown that statins reduce CV events.[14,18,19,83] Meta-analysis of key statins by Nayak et al. also revealed the post-trial legacy effects of statins on CVD mortality and all-cause mortality in primary prevention.[84] However, recent advancement of understanding of signaling molecules, genetics and analytical tools has shifted the focus of lipid-lowering targets to a proprotein convertase subtilisin/kexin type 9 (PCSK9) protein, which is primarily produced in hepatocytes.[85-89] The PCSK9 protein binds to the low

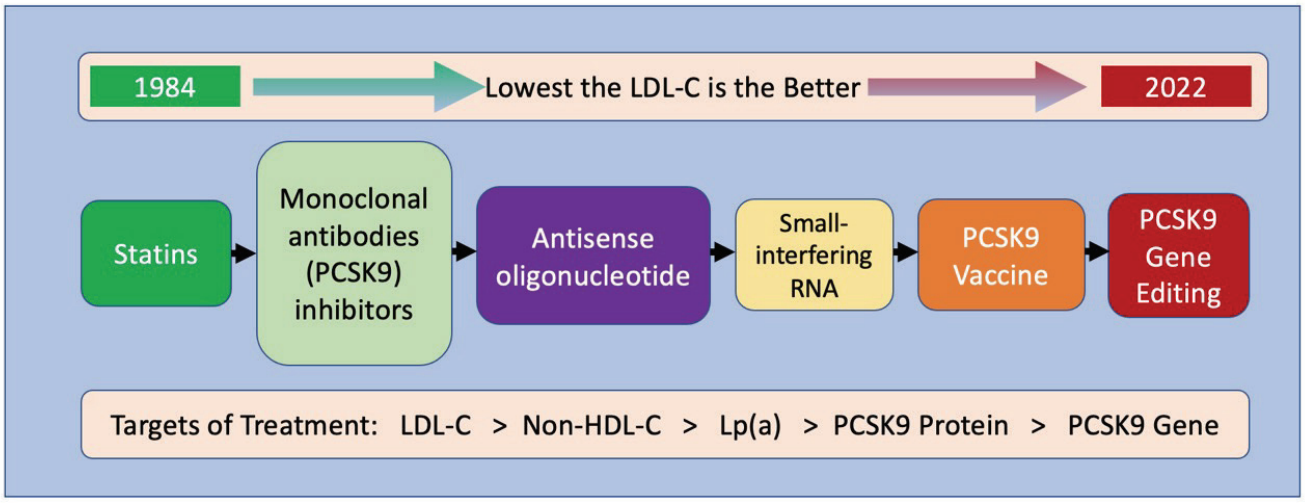
density lipoprotein receptors (LDL-R) on the surface of hepatocytes and blocks the recirculation of LDL-R by enhancing its lysosomal degradation.[90] LDL-R on hepatocytes generally scavenge circulating LDL-C particles and transport them into hepatocytes. By inhibiting PCSK9, the destruction of LDL-R is interrupted,[90] thereby allowing the presence of increased LDL-R on surface of hepatocytes. This in turn causes more LDL-C particles to be removed from circulation. Recent data on monoclonal antibodies, which bind to PCSK9 protein, have shown profound reduction in LDL-C resulting in significant CV outcome benefits in secondary prevention trials.[44,47] The PCSK-9 antibodies are generally given twice a month subcutaneously but remain costly, limiting affordability and thus long-term adherence. Recently, small interfering RNA (si-RNA), such as inclisiran, which reduces the hepatic synthesis of PCSK9 protein, was studied in ORION 10 and ORION 11 phase III randomized controlled trials and showed up to 50% reduction in LDL-C.[91]

significant and sustained lowering of LDL-C in primates.[93] Since the first randomized controlled trial of statins in 1984, lipid-lowering strategies have shifted to biological and RNA-directed approaches over the last few decades, and most recently, gene editing tools have joined the arsenal of lipid management with the aim of profound and sustained lowering of LDL-C **(Figure 2).** However, the efficacy, safety, and translational research data of these newest RNA- and gene- directed lipid lowering therapies in humans are still pending

Conclusions

Since ASCVD is a life-long progressive disease, a clear consensus is now emerging to initiate lipid lowering treatment earlier in life to prevent development of ASCVD and halt disease progression. Currently, there is a significant gap between guideline recommendations and achieving the target LDL-C lowering goal in patients. Along with lifestyle modifications, healthy diet and exercise, primary prevention is focusing on LDL-C management with the following principle: "the earlier, lower, and longer, the better." It is well-known that current risk scoring models can both under- and over-estimate CV risk. New generation imaging modalities, such as high-resolution, low-radiation CCTA, are becoming more adept at identifying high-risk individuals. Primary prevention should focus not only on high-risk individuals but also be broadened to include low and intermediate-risk groups which comprise the majority of the population to achieve a large scale ASCVD

Figure 2. Strategies of Lipid Lowering Therapies



LDL-C, low density lipoprotein cholesterol; Non-HDL-C, non high density lipoprotein cholesterol; Lp(a), lipoprotein (a); PCSK9, proprotein convertase subtilisin/kexin type 9.

The advantage of si-RNA is twice a year administration and lower cost compared to PCSK9 monoclonal antibodies. In addition, several preclinical studies have focused on PCSK9 vaccines which will induce production of autoantibodies against the PCSK9 protein, thereby decreasing the degradation of LDL-R.[92] Recently, gene editing technology, such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) editing tool is being used to target the PCSK9 gene. Musunuru et al. demonstrated that CRISPR base editing of PCSK9 gene had caused a

mortality and morbidity benefit. Most importantly, management of CV risk factor should be individualized and patient-centered with an emphasis on physician-patient communication. Future lipid-lowering therapies including PCSK9 vaccines and gene editing therapies are highly promising. However, their safety, efficacy, and outcome benefits in humans have yet to be proven.

Key Points

- ASCVD is a life-long vascular remodeling process.
- Earlier initiation of lipid lowering treatment, lower LDL-C, and longer the treatment is associated with improved CV outcomes.
- Physician-patient communication should be proactive to decrease the gap between guideline-directed recommendations and day-to-day practice.
- Lipid-lowering treatment strategies have shifted to targeting the PCSK9 protein, which plays an integral role in the availability of LDL-R which remove LDL-C from circulation.
- Production of native PCSK9 antibody by a PCSK9 vaccine, interruption of PCSK9 production by small interfering RNA or PCSK9 gene editing technology are promising future therapies which could halt and potentially eradicate ASCVD. However, their safety, efficacy, and outcome benefits in humans are yet to be proven.

Declarations

Conflict of Interest

Dr. Azizul Hoque has nothing to disclose.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

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