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Lipid-lowering therapies in patients undergoing percutaneous coronary intervention

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Abstract

Cardiovascular disease is the leading cause of death worldwide. Over past decades, multiple clinical trials have provided substantial evidence supporting the advantages of managing plasma lipids in individuals with coronary artery disease (CAD). A primary focus in reducing clinical atherosclerotic cardiovascular disease (ASCVD) in patients who have undergone percutaneous coronary intervention (PCI) is the regulation of blood lipids, with an emphasis on low-density lipoprotein (LDL) cholesterol. Statins represent the cornerstone of lipid-lowering therapy (LLT), with high-intensity statins consistently associated with beneficial outcomes in patients at high risk of ASCVD. Nevertheless, a notable portion of patients do not achieve their target cholesterol levels through statin monotherapy, necessitating the inclusion of complementary LLT strategies. Among these therapies are ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors, which have also demonstrated clinical advantages by further reducing cholesterol levels. Existing guidelines recommend using these agents when maximally tolerated statin doses fall short of achieving target LDL levels. Additionally, recently introduced ATP-citrate lyase inhibitors, such as bempedoic acid, have gained approval as adjunctive treatments. Furthermore, icosapent ethyl, a purified derivative of eicosapentaenoic acid, targets hypertriglyceridemia and has shown cardiovascular benefits compared to placebo. In this article, we delve into the mechanisms of blood lipids and molecular targets in connection with CAD undergoing PCI. We also explore the current landscape of available LLT options, guidelines in practice, and the subtleties of therapy.

Keywords: 3-hydroxy-methylglutaryl coenzyme A inhibitors, cardiovascular disease, ezetimibe, familial hypercholesterolemia, hypertriglyceridemia, icosapent ethyl, low-density lipoprotein, non-statin lipid-lowering therapies, PCSK9 inhibitors

INTRODUCTION

Cardiovascular disease persists as the predominant cause of global burden of mortality and morbidity worldwide, steadily increasing up to 19.7 million in 2019[1,2]. The cholesterol hypothesis posits that elevated blood cholesterol levels constitute a significant risk factor for atherosclerotic cardiovascular disease (ASCVD) and reducing cholesterol levels will consequently lower the risk of ASCVD[3,4]. Support for the idea that serum cholesterol plays a role in ASCVD is derived from studies on animals, genetic manifestations of hypercholesterolemia, epidemiological investigations, and randomized controlled trials. The formation of atherosclerotic, lipid-laden plaques from serum cholesterol contributes to blood vessel blockage and is ultimately responsible for the progression of cardiovascular disease.

In recent decades, outcome trials have presented substantial backing for the advantages of managing plasma lipids in individuals with coronary artery disease (CAD). Treatments aimed at lowering lipid levels have demonstrated their effectiveness in decelerating the advancement of atherosclerotic disease[5]. This finding further reinforces the pathophysiological connections between plasma lipids and the progression of CAD. Among non-lipid mechanisms involved in reducing CAD progression, lipid-lowering drugs have also been implicated in plaque stabilization, reduced inflammation, reversal of endothelial dysfunction, and decreased thrombogenicity[6].

In this review, we will examine the available lipid-lowering therapies currently being offered to patients. We will discuss mechanisms of action, current guidelines, and nuances of therapy. Importantly, the utility of these therapies in patients with CAD undergoing percutaneous coronary intervention (PCI), particularly concerning periprocedural and long-term mortality outcomes, will be suggested. *Note to reader: All expanded trial names can be found in Table 1.

THE MOLECULAR TARGET

Treatment targets

Previous epidemiological investigations have revealed a connection between total cholesterol levels and the occurrence of coronary heart disease (CHD) and CHD-related mortality. Specifically, low-density lipoprotein (LDL) cholesterol has traditionally served as an assessment tool for cardiovascular risk and is frequently utilized as a surrogate marker for coronary vascular disease risk[7,8]. LDL is derived from very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and LDL remnants. Non-high-density lipoprotein cholesterol, which includes LDL, exhibits a nearly log-linear relationship with the incidence of cardiovascular disease[9]. In past decades, studies have consistently shown that reducing LDL levels significantly diminishes the risk of CHD, and it has been approximated that a 1.0 mmol/L reduction in LDL results in a 22% decrease in ASCVD risk[8]. As a result, LDL has become the primary target of lipid-lowering therapy. Current guidelines established by the American Heart Association and American College of Cardiology (AHA/ACA) and the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) recommend LDL cholesterol (LDL-C) as an essential biomarker to set up treatment goals[9-11]. LDL-C concentrations are highly concordant with LDL particles, but in certain situations such as diabetes, obesity, or very low LDL-C, the relationship between LDL-C concentration and LDL particles is discordant. In that case, LDL particles per se determine the accurate risk of CHD[10,12-14].

Apolipoprotein B (ApoB) is a crucial component of atherogenic lipoproteins. ApoB levels represent the concentration of the atherogenic particle in LDL, IDL, VLDL, and lipoprotein (a) independent of their

Table 1. Major clinical trials on lipid-lowering therapy

Trial name	Abbreviation	Class	Population	Experimental arm	Control arm	Primary outcome
Scandinavian simvastatin survival study[33]	4S	Statin	CHD	Simvastatin	Placebo	Mortality
Cholesterol and recurrent events[34]	CARE	Statin	MI	Pravastatin	Placebo	Fatal coronary event or a nonfatal MI
Long-term intervention with pravastatin in ischemic disease[35]	LIPID	Statin	History of AMI and UA	Pravastatin 40 mg	Placebo	Death from CHD
Osaka acute coronary insufficiency study-LIPID[37]	OACIS-LIPID	Statin	MI	Pravastatin	Placebo	Composite of death, nonfatal MI, UA, stroke
GREek atorvastatin and coronary-heart-disease evaluation[38]	GREACE	Statin	CHD	Atorvastatin 10-80 mg	Usual medical care	Death, nonfatal MI, UA, CHF revascularization, stroke
Aggressive lipid-lowering initiation abates new cardiac events[39]	ALLIANCE	Statin	Hyperlipidemia	Atorvastatin 80 mg or LDL-C < 80 mg	Usual medical care	Cardiac event
Treating to new targets[40]	TNT	Statin	CHD	Atorvastatin 80 mg or LDL-C < 80 mg	Atorvastatin 10 mg	Death from CHD, nonfatal non-procedure-related MI, resuscitation after cardiac arrest, stroke
High-Dose *vs.* low-dose pitavastatin in Japanese patients with stable coronary artery disease[41]	REAL-CAD	Statin	Stable CAD	Pitavastatin 4 mg	Pitavastatin 1 mg	Composite of CV death, nonfatal MI, nonfatal ischemic stroke, UA
Antihypertensive and lipid-lowering treatment to prevent heart attack trial[42]	ALLHAT-LLT	Statin	LDL 120-189 mg/dL (100-129 mg/dL if CHD)	Pravastatin	Usual medical care	All-cause mortality
High-dose atorvastatin *vs.* usual-dose simvastatin for secondary prevention after myocardial infarction[43]	IDEAL	Statin	Previous MI	Atorvastatin 80 mg	Simvastatin 20 mg	Major coronary event (coronary death, nonfatal MI, cardiac arrest with resuscitation)
Reversal of atherosclerosis and aggressive lipid lowering[45]	REVERSAL	Statin	CHD	Atorvastatin 80 mg	Pravastatin 40 mg	Athoeroma volume
Myocardial ischemia reduction with aggressive cholesterol lowering[49]	MIRACL	Statin	ACS	Atorvastatin 80 mg	Placebo	Death, nonfatal MI, cardiac arrest with resuscitation or recurrent symptomatic myocardial ischemia requiring hospitalization
Aggrastat to zocor: phase Z[51]	A to Z: phase Z	Statin	ACS	Simvastatin 40 mg 1 month followed by 80 mg	Placebo 4 months followed by 20 mg simvastatin	CV death, nonfatal MI, readmission for ACS and stroke
Pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial Infarction[52]	PROVE IT-TIMI 22	Statin	ACS	Atorvastatin 80 mg	Pravastatin 40 mg	Composite of death from any cause, MI, UA requring revascularization
Atorvastatin for reduction of myocardial damage during angioplasty[53]	ARMYDA	Statin	Chronic stable angina	Atorvastatin 40 mg	Placebo	Postprocedural MI
Efficacy of high-dose atorvastatin loading before primary percutaneous coronary intervention in ST-elevation myocardial infarction[56]	STATIN-STEMI	Statin	STEMI	Pretreatment of atorvastatin 80 mg	Pretreatment of atorvastatin 10 mg	Death, nonfatal MI and target vessel revascularization
Novel approaches for preventing or limiting events[57]	NAPLES II	Statin	Symptomatic CAD	Atorvastatin 80 mg	Placebo	Periprocedural MI
Rosuvastatin pretreatment in patients undergoing elective percutaneous coronary intervention to reduce the incidence of myocardial periprocedural necrosis[58]	ROMA	Statin	Stable angina	Rosuvastatin 40 mg	Standard treatment	Periprocedural myocardial necrosis

Early statin treatment in patients with acute coronary syndrome[59]	ESTABLISH	Statin	ACS	Atorvastatin 20 mg	Placebo	Change in plaque volume
Reduction of cholesterol in ischemia and function of the endothelium[60]	RECIFE	Statin	ACS	Pravastatin 40 mg	Placebo	FMD
Improved reduction of outcomes: vytorin efficacy international[61]	IMPROVE-IT	Ezetimibe	ACS	Ezetimibe 10 mg plus Simvastatin 40 mg	Simvastatin 40 mg	Composite of CV death, nonfatal MI, UA requring rehospitalization, coronary revascularization
Further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk[71]	FOURIER	PCSK9 inhibitor	ASCVD	Evolocumab plus statin	Statin	Composite of CV death, MI or stroke
Evaluation of cardiovascular outcomes after an acute coronary syndrome during treatment with alirocumab[72]	ODYSSEY-OUTCOMES	PCSK9 inhibitor	ACS	Alirocumab plus statin	Statin	Composite of death from CHD, nonfatal MI, ischemic stroke, UA requiring hospitalization
Global assessment of plaque regression with a PCSK9 antibody as measured by intravascular ultrasound[78]	GLAGOV	PCSK9 inhibitor	CAD	Evolocumab plus statin	Statin	Change in PAV
Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol[86]	ORION 10, 11	PCSK9 inhibitor	ASCVD	Inclisiran plus statin	Statin	Percent change in LDL-C
Cholesterol lowering via bempedoic acid, an ACL-inhibiting regimen[88]	CLEAR	Bempedoic acid	High risk for CVD (unable to take statin)	Bempedoic acid	Placebo	CV death, nonfatal MI, nonfatal stroke, coronary revascularization
Randomized evaluation of the effects of anacetrapib through lipid modification[96]	REVEAL	CETP inhibitor	ASCVD	Anacetrapib	Placebo	Composite of coronary death, MI, coronary revascularization
Heart institute of Japan-proper level of lipid lowering with pitavastatin and ezetimibe in acute coronary syndrome[113]	HIJ-PROPER	Ezetimibe	ACS	Pitavastatin plus ezetimibe	Pitavastatin	Composite of all-cause death, nonfatal MI, nonfatal stroke UA, ischemia-driven revascularization
Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia[24]	REDUCE IT	Icosapent ethyl	CVD or CV risk factors	Icosapent ethyl plus statin	Statin	Composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization or UA

ACL: ATP-citrate lyase; ACS: acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; CAD: coronary artery disease; CHD: coronary heart disease; CVD: cardiovascular disease; FMD: flow-mediated dilatation; LDL: low-density lipoprotein; MI: myocardial infarction; PCSK9: proprotein convertase subtilisin/kexin type 9; UA: unstable angina.

cholesterol content. Indeed, it has been demonstrated that the number of serum ApoB particles present within the arterial wall is linked to the risk of cardiovascular disease. Therefore, cardiovascular risk may be more directly associated with the quantity of ApoB particles than the amount of cholesterol they contain[15,16]. This has led to the argument that ApoB may serve as a better indicator of cardiovascular risk compared to other cholesterols[17]. In line with this, the 2019 guidelines established by ESC/EAS outlined the usefulness of ApoB as a more precise marker of cardiovascular risk compared to other cholesterols and presented ApoB levels as one of the treatment targets of lipid management in ASCVD including patients undergoing PCI[10].

There has also been a demonstrated correlation between elevated triglycerides (TG) and an increased risk of cardiovascular disease (CVD)[18,19]. However, it is unclear whether hypertriglyceridemia directly causes CVD, or if triglycerides act as a proxy for coexisting metabolic derangements[20]. Elevated serum triglyceride levels can result from isolated increases in chylomicron concentration, an upsurge in the triglyceride content of VLDL, or a rise in the total number of circulating VLDL particles. Consequently, hypertriglyceridemia should be regarded as a non-specific condition, possibly entailing varying degrees of

cardiovascular risk[21]. Nonetheless, TG and TG-rich lipoprotein (TGRL) are regarded as major contributors to ASCVD risk even in patients who achieved guideline-recommended LDL levels, and a reduction in serum triglycerides has been linked to an additional reduction of significant cardiovascular events[22,23]. As a result, potential therapeutic benefits remain associated with medications such as icosapent ethyl (IPE), fibrate, and omega-3 fatty acids. Notably, the use of IPE exhibited a significant reduction in ischemic events among individuals who have established ASCVD and elevated triglycerides, as discussed later in this review[24].

LIPID-LOWERING THERAPIES

Non-pharmacologic interventions

Non-pharmacological management of dyslipidemia plays a crucial role in both primary and secondary prevention. The National Cholesterol Education Program (NCEP) guidelines outline three key pillars of non-pharmacological management, which include dietary adjustments, physical activity, and weight maintenance. These interventions have the potential to serve as effective treatments for as many as 90% of patients affected by dyslipidemia[25]. Various nutrients have been associated with pro-atherosclerotic risk factors, such as hypertension, obesity, and dyslipidemia[26]. Elevated cholesterol levels are often a result of increased consumption of saturated fats and dietary cholesterol. Research has demonstrated that regular consumption of foods rich in saturated fats leads to higher levels of LDL cholesterol in the bloodstream, coupled with an increase in high-density lipoprotein (HDL) levels[27]. In contrast, unsaturated fats tend to improve the lipid profile by reducing LDL levels, with minimal effects on HDL[10]. The NCEP Step I and Step II dietary plans have been designed to progressively decrease the consumption of calories and saturated fats, thereby reducing lipoprotein levels and enhancing weight loss. The significance of dietary modifications should be underscored, as even a 1.0 mmol/L reduction in low-density cholesterol can potentially lower an individual's risk of developing CAD by 20%[10,28].

In addition to cutting down on saturated fat intake, increasing the consumption of soluble fiber has been demonstrated to reduce both total cholesterol and LDL cholesterol levels. An additional 3 grams of soluble fiber per day may potentially reduce total cholesterol by 5-6 mg/dL. The AHA diet, which places an emphasis on dietary fiber, has the potential to lower total cholesterol by 11%-32%. Furthermore, a diet high in carbohydrates and fiber can help lower serum triglyceride levels while elevating HDL levels[10].

Exercise is another essential element in the management of dyslipidemia. Most patients can benefit from engaging in aerobic exercise for at least 30 min, a minimum of four times per week[10].

In the same vein, the NCEP also advocates weight loss as a fundamental component of cholesterol management. Research has shown that a 5%-10% reduction in body weight can lead to improvements in cardiovascular risk factors by lowering triglycerides, total cholesterol, and LDL cholesterol. Additionally, individuals who lose more than 10% of their body weight experience even more significant reductions in serum lipids and a potential elevation in HDL cholesterol. Moreover, various lifestyle changes can impact atherogenesis and cardiovascular risk factors. The AHA underscores the importance of quitting smoking and vaping, as these habits have been linked to decreased HDL levels and its function, increasing the risk of cardiovascular disease[9].

Atherogenesis is known to be partially influenced by the oxidation and glycosylation of LDL cholesterol. Consequently, antioxidants, such as vitamin C, E, and beta-carotene, may offer some protection against atherogenesis[29].

Lipid-lowering drug therapies

Statins-mechanism of action and cardiovascular benefits

Statins represent one of the most extensively studied drug classes in randomized controlled trials. They function by reducing LDL cholesterol levels through the inhibition of 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase, a mechanism known for its role in curbing the growth and instability of coronary plaques, ultimately lowering the risk of major cardiovascular events. Statins have also been implicated in improving endothelial function and reducing inflammation and thrombogenicity[10].

The safety and efficacy of commonly used statins, which include atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin, are well-established. While all statins operate through a shared mechanism, there are slight variations in their pharmacokinetic properties and susceptibility to interactions. Statins are categorized based on their intensity, which can differ depending on the dosage. High-intensity statins achieve LDL reductions of 50% or more, while moderate-intensity statins result in a 30%-60% LDL reduction, and low-intensity statins, a less than 30% reduction[9,10,30]. Statins categorized by intensity and dosage can be visualized in Table 2[9,10].

More intensive statin therapy has been associated with an increased side effect profile[31,32]. A meta-analysis from 135 randomized controlled trials examined the tolerability of various statins[31]. This analysis found that simvastatin and pravastatin had the lowest likelihood of causing myalgia, elevated transaminases, and creatine kinase (CK) elevation compared to other statins. With regards to transaminitis, pravastatin, rosuvastatin, and simvastatin demonstrated a reduced likelihood of transaminase elevation, while atorvastatin and fluvastatin showed higher odds. The analysis also revealed that, as a class, statins did not significantly differ from control groups in terms of CK elevation. However, at the meta-analysis level, statins as a class exhibited a statistically significant association with the incidence of diabetes mellitus compared to placebo. Pravastatin and simvastatin emerged as the statins with the most favorable profile in terms of tolerability and side effects[31].

Historically, the 4S study marked a pivotal moment as the first large-scale randomized controlled trial to showcase a reduction in major cardiovascular events, cardiovascular mortality, and overall mortality in individuals with CAD and elevated cholesterol levels who were administered simvastatin, compared to those given placebo[33]. Following this landmark trial, the CARE trial demonstrated the protective effects of 40 mg pravastatin, compared to a placebo, in patients who had experienced a myocardial infarction (MI) and had average cholesterol levels[34]. The LIPID trial also unveiled the durable benefits of lowering LDL in patients with a wide spectrum of cholesterol levels and a history of MI or unstable angina (UA). This reduction ultimately decreased mortality risk from CHD and all-cause death[35].

Likewise, the MRC/BHF Heart Protection Study illustrated a notable decrease in the incidence of major vascular events in a diverse group of high-risk individuals who took 40 mg of simvastatin compared to placebo. This included statistically significant reductions in all-cause mortality, coronary death rate, nonfatal MI or coronary deaths, nonfatal or fatal strokes, and coronary or non-coronary revascularization. Importantly, these benefits were observed irrespective of initial cholesterol levels[36]. Another study showed a notable reduction in recurrent major adverse cardiac events (MACE), including death, nonfatal MI, UA, stroke, revascularization, and rehospitalization. This reduction was observed in patients with acute MI who were administered 10 mg of pravastatin compared to those receiving non-statin lipid-lowering drugs. The event rate was 17.9% in the statin group and 31.4% in the control group. Additionally, the statin group exhibited a 22% reduction in LDL from baseline, compared to a 6% reduction in the control group[37].

Table 2. High-, moderate-, and low-intensity statin therapy by dosage

Strength	Name	Dose
High-intensity		
	Atorvastatin	40-80 mg
	Rosuvastatin	20-40 mg
Moderate-intensity		
	Atorvastatin	10-20 mg
	Fluvastatin	40 mg (or XL 80 mg)
	Lovastatin	40-80 mg
	Pitavastatin	1-4 mg
	Pravastatin	40-80 mg
	Rosuvastatin	5-10 mg
	Simvastatin	20-40 mg
Low-intensity		
	Fluvastatin	20-40 mg
	Lovastatin	20 mg
	Pravastatin	10-20 mg
	Simvastatin	10 mg

Intensity of statins

The utilization of moderate- and high-intensity statins has been proven to yield significant clinical benefits across a wide spectrum of patients compared to low-intensity therapy. Findings from the GREACE study emphasized that the treatment of CHD patients with atorvastatin (primarily 20 mg atorvastatin) to attain NCEP lipid targets (less than 100 mg/dL) is not only safe but also leads to a substantial decrease in total mortality, as well as coronary mortality and morbidity and stroke, compared to standard care involving non-statin lipid-lowering drugs. In this study, patients who received atorvastatin, with doses titrated to achieve an LDL goal of less than 100 mg/dL (< 2.586 mmol/L) among CHD patients, experienced a statistically significant reduction in primary endpoints (indicative of coronary morbidity and mortality). Importantly, there was a statistically significant mean LDL difference between the intervention and control groups by the end of the follow-up period, with an LDL reduction from baseline of 46% in the treatment group compared to 5% in the control group[38].

Several trials have also demonstrated that achieving lower LDL levels is associated with fewer MACE in patients with pre-existing CHD. The ALLIANCE study, involving 2,442 CHD patients with comorbid hyperlipidemia, initiated either an aggressive atorvastatin regimen titrated to achieve an LDL goal of less than 80 mg/dL (2.069 mmol/L) or a maximum daily dose of 80 mg, as opposed to receiving usual care (other non-statin lipid-lowering drugs). Their result showed that both the time to adverse cardiovascular events (high-intensity atorvastatin vs. usual care, 23.7% *vs.* 27.7%) and LDL cholesterol levels (atorvastatin *vs.* usual care, 34.3% *vs.* 23.3%) may be reduced with an aggressive atorvastatin regimen[39]. Likewise, the TNT trial showed that employing intensive atorvastatin therapy to reduce LDL levels below 100 mg/dL correlates with considerable clinical benefits in patients with stable CHD[40]. The REAL-CAD trial also demonstrated a significant reduction in MACE with higher-intensity statins in Asian populations[41].

Interestingly, some trials failed to show a significant reduction in MACE when comparing patients on statins to those without lipid-lowering therapy, even when there was a significant reduction in LDL cholesterol levels. For instance, the ALLHAT-LLT study, comparing pravastatin 40 mg *vs.* placebo, revealed the efficacy of statins in patients with stage 1 or 2 hypertension and at least one additional CHD risk factor. The study demonstrated that adherence to pravastatin resulted in a 28% reduction in LDL levels from

baseline, compared to an 11% reduction in the control group. However, dissimilar to previous trials, no reduction in total mortality was observed[42]. The IDEAL study was also unable to establish a statistically significant reduction in MACE in patients taking high-intensity statins despite a significant 49% reduction in LDL concentration compared to the moderate-intensity group[43]. However, in a meta-analysis from Cholesterol Treatment Trialist Collation (CTT) comprising 26 RCTs evaluating high- *vs.* moderate-intensity statin therapy, more intensive regimens produced a significant 15% reduction in major vascular events. Additionally, the cardiovascular benefits per 1.0 mmol/L reduction in LDL cholesterol were similar to findings from previous statin *vs.* control trials[44].

Stable CAD and acute coronary syndrome

The use of high-intensity statins not only reduces the occurrence of periprocedural myocardial necrosis and risk of MACE but also hinders the progression of atherosclerosis. This effect on atherosclerosis has been observed in patients with stable CAD as well as in those who have undergone coronary artery bypass graft (CABG) surgery[45,46]. Additionally, this reduced rate of atherosclerosis has been linked to decreased carotid intimal-medial thickening[47,48].

The REVERSAL study utilized intravascular ultrasound (IVUS) to assess the advancement of atherosclerosis in 654 CAD patients undergoing coronary angiography. These patients were either on an intensive statin regimen (atorvastatin 80 mg) or a moderate-intensity regimen (pravastatin 40 mg). The study revealed that coronary atherosclerosis progressed in the pravastatin group by a 2.7% increase, while no progression was observed in the atorvastatin group (0.4% decrease without statistical significance) compared to the baseline measurements[45].

Previous trials have demonstrated that initiating statin therapy in the post-acute coronary syndrome (ACS) period has a role in reducing the incidence of post-ACS MACE. The MIRACL study, for example, revealed that treatment with atorvastatin 80 mg daily, initiated during the acute phase of UA or non-Q wave MI, leads to a reduction in the risk of early recurrent ischemic events. The reduction was notable compared to a placebo, with a 16 week follow-up showing rates of 14.8% in the atorvastatin group *vs.*17.4% in the placebo group[49]. In addition, the follow-up to the Extended-ESTABLISH study showed that the in-hospital initiation of statins promptly following an ACS event provides longstanding benefits, particularly in reducing the occurrence of major adverse cardiac and cerebrovascular events (MACCE). The atorvastatin group displayed significantly higher cumulative event-free survival than the control group (lipid-lowering diet).

Early statin administration was also identified as a strong predictor of MACCE[50]. The importance of early statin initiation was further underscored by the A to Z: Phase Z trial. A comparison of early initiation of an intensive statin regimen to delayed initiation of a less-intensive regimen in ACS patients indicated that early initiation resulted in a reduction in MACE, although it did not reach statistical significance (simvastatin *vs.* placebo, 14.4% *vs.* 16.7%)[51]. The PROVE IT-TIMI 22 trial provided further evidence that, with early initiation of high-intensity statin after ACS, patients experience an increased significant reduction in MACE when their target LDL level is set lower than the original guideline target of 100 mg/dL. In this trial, high-dose atorvastatin (80 mg) compared to standard-dose pravastatin (40 mg) reduced the hazard ratio for MACE by 16%[52].

Timing of statin in PCI

The implementation of higher-intensity statins in the pre-procedural period has also been shown to enhance clinical outcomes. The first of the ARMYDA series of trials demonstrated that in patients with

stable angina, pretreatment with atorvastatin at a daily dose of 40 mg for one week prior to coronary intervention can reduce the occurrence of periprocedural MI compared to placebo[53]. Furthermore, the ARMYDA-ACS trial revealed that short-term pretreatment with atorvastatin before PCI leads to improved clinical outcomes in patients with UA and non-ST-segment elevation myocardial infarction (NSTEMI). Patients who received a 12-h pretreatment dose of atorvastatin at 80 mg, followed by an additional pre-procedure dose, exhibited a statistically significant reduction in periprocedural and post-PCI MACE compared to those who received a placebo[54]. Finally, the ARMYDA-RECAPTURE trial showed that a short-term, high-dose atorvastatin pre-load before PCI improves outcomes during and after PCI in patients who are already on long-term statin therapy. Patients receiving a 12-h pretreatment dose of atorvastatin at 80 mg before the intervention, along with an additional 40 mg pre-procedural dose, experienced a significant decrease in MACE following PCI, compared to those who received pre-procedural placebo prior to intervention, followed by treatment with atorvastatin 40 mg after the index procedure[55].

In addition to the ARMYDA series of trials, the STATIN-STEMI trial demonstrated increased myocardial perfusion in ST-elevation myocardial infarction (STEMI) patients undergoing PCI. While the STATIN-STEMI trial did not show a significant reduction in MACE in patients taking pre-procedural atorvastatin at 80 *vs.* 10 mg, it is worth noting that the corrected thrombolysis in myocardial infarction (TIMI) frame count was significantly reduced in the atorvastatin 80 mg compared to 10 mg group (26.9% *vs.* 34.1%)[56].

The NAPLES II trial also offered evidence supporting the cardioprotective effect of a single loading dose of high-intensity atorvastatin (80 mg) given within 24 h of stent placement. In individuals who had not previously taken statins, the administration of a pretreatment dose of atorvastatin 80 mg before elective PCI, as compared to no statin pretreatment, was linked to a statistically significant reduction in the incidence of periprocedural MI (9.5% *vs.* 15.8%)[57].

Other high-intensity statins, particularly rosuvastatin, have also demonstrated their effectiveness in reducing periprocedural MI, as evident in the results of the ROMA trial. The ROMA study revealed that a single high-intensity loading dose of rosuvastatin at 40 mg within 24 h of elective PCI significantly reduces the occurrence of periprocedural MI at both the 12- and 24-h marks after intervention compared to standard care (non-statin lipid-lowering therapy)[58].

Additionally, the ESTABLISH trial provided evidence that in patients with ACS undergoing emergent PCI, early and aggressive lipid-lowering therapy using atorvastatin for 6 months leads to a significant reduction in plaque volume, as measured by IVUS, in comparison to the control group (13.1% decrease *vs.* 8.7% increase). Furthermore, the atorvastatin group experienced a substantial reduction in LDL cholesterol compared to standard care (-41.7% *vs.* 0.7%)[59].

The impact of statins on the improvement of endothelial function following ACS has been demonstrated in the RECIFE trial. In patients with acute MI or UA and elevated total and LDL cholesterol levels, endothelium-dependent flow-mediated dilatation (FMD) was measured after treatment with either placebo or pravastatin at 40 mg for 6 weeks. In this study, FMD showed a notable increase in the pravastatin group (from 4.93% to 7.0%), whereas the placebo group did not exhibit such significant changes. The pravastatin group showed a significant reduction in total (23% decrease) and LDL (33% decrease) cholesterol levels, but not in the placebo group[60].

Ezetimibe

As mentioned earlier, the addition of ezetimibe to a statin regimen has proven effective in achieving lower cholesterol and reducing the risk of cardiovascular disease. The IMPROVE-IT trial, which included about 70% of patients who underwent PCI, provided compelling evidence for the incorporation of ezetimibe into statin therapy. For stable patients who had recently experienced an ACS event, and whose LDL levels fell within guideline recommendations, ezetimibe plus simvastatin 40 mg led to a further reduction in LDL levels and MACE compared to simvastatin alone[61]. Another study evaluating the effect of ezetimibe in elderly patients (≥ 75 years old) with no prior cardiovascular history, indicated that reduction of LDL cholesterol with ezetimibe contributed to the prevention of cardiovascular events in the elderly population[62]. In a comprehensive systematic review and meta-analysis, substantial evidence supports the efficacy of ezetimibe in reducing ASCVD risk and suggests that moderate-density statin plus ezetimibe combination therapy may be more effective and safe than high-intensity statin in terms of reduction of LDL cholesterol and statin-related adverse effect[63,64].

PCSK9 inhibitors

In addition to statin and ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors play a crucial role in regulating cholesterol metabolism. PCSK9 binds to low-density lipoprotein receptors (LDLR) on hepatocytes, promoting LDLR degradation in the liver, thereby increasing serum LDL levels. Increased PCSK9 activity has been associated with elevated LDL cholesterol levels. Indeed, familial hypercholesterolemia (FH) has been linked to gain-of-function mutations in PCSK9[65,66]. Conversely, a reduction in PCSK9 function has been linked with lower cholesterol levels and, in turn, a reduced risk of cardiovascular disease[67]. PCSK9 inhibitors prevent PCSK9 from binding to LDL, leading to a decrease in circulating LDL levels[68].

Alirocumab is a human monoclonal immunoglobulin of the G1 isotype, while evolocumab belongs to the G2 isotype. Both act to bind to human PCSK9, leading to a reduction in LDL[68,69]. Both alirocumab and evolocumab are administered as subcutaneous injections with the indication of reducing the risk of MI and cerebrovascular accident (CVA). They share a similar safety profile, although a comprehensive meta-analysis has indicated that alirocumab is associated with a higher risk of injection site reaction than evolocumab[70]. A number of significant trials have provided substantial evidence for both the short-term and long-term advantages of alirocumab and evolocumab in reducing the occurrence of cardiovascular events. The FOURIER trial illustrated the cardiovascular benefits of lowering LDL cholesterol levels below existing targets. Particularly, when administered in conjunction with statin therapy, evolocumab reduced LDL levels to a median of 30 mg/dL and the risk of MACE by 15% in patients with pre-existing CAD, compared to placebo[71]. The ODYSSEY-OUTCOMES study further showcased the effectiveness of alirocumab in individuals with a recent history of ACS (PCI or CABG performed in about 71%) whose atherogenic lipoprotein levels remained elevated, despite treatment with either high- or maximum-dose statin therapy. In this trial, alirocumab exhibited lower MACE rates compared to the placebo group (9.5% *vs.* 11.1%)[72]. Subsequent trials within the ODYSSEY series have provided further insight into the efficacy of PCSK9 inhibitors in high-risk ASCVD patients in reducing cardiovascular disease risk and cholesterol levels, all while maintaining a well-tolerated side effect profile[73-76]. These effects have also been observed in patients with type 2 diabetes mellitus (T2DM) and mixed dyslipidemia, even when receiving maximum statin therapy, in comparison to usual care (non-statin lipid-lowering therapies)[77].

The GLAGOV trial, encompassing 968 CAD patients, showed significantly greater LDL cholesterol lowering and atheroma regression in patients taking PCSK9 inhibitors compared to placebo. Patients on an evolocumab regimen combined with a pre-existing statin achieved markedly lower LDL levels

(-56.6 mg/dL) and a substantial reduction in percent atheroma volume (PAV) (-1.0%)[78].

Moreover, as with the prompt initiation of statins after ACS, the immediate commencement of PCSK9 inhibitors alongside high-intensity statin therapy has also demonstrated a significant decrease in LDL cholesterol levels compared to statin therapy alone[79].

Another extensive meta-analysis provides compelling data supporting the effectiveness of both alirocumab and evolocumab in reducing MACE[80]. In a systematic review of randomized trials on non-statin lipid-lowering therapies, both alirocumab and evolocumab have demonstrated efficacy in improving lipid levels, but alirocumab appears to be more effective in patients at high cardiovascular risk who have not achieved their LDL goals. Evolocumab has shown superior efficacy in patients with heterozygous FH. However, when HDL levels were analyzed, it was determined that both evolocumab and alirocumab resulted in a moderate increase in HDL from baseline compared to placebo and ezetimibe[81].

Inclisiran, on the other hand, is a small interfering double-stranded RNA (siRNA) that specifically inhibits the hepatic production of PCSK9. The antisense strand of inclisiran corresponds to human PCSK9 mRNA. Incrisiran is conjugated with triantennary N-acetylgalactosamine carbohydrates (tri-GalNAC) to bind asialoglycoprotein receptors on the surface of hepatocytes. This enables uptake of the drug, and in the hepatocyte, inclisiran binds to the RNA-silencing complex (RISC) to cleave the mRNA encoding PCSK9. This consequently lowers serum LDL cholesterol levels[82].

Inclisiran has proven its efficacy in reducing LDL cholesterol levels in phase 1 and phase 2 trials, with reductions ranging from 27.9% to 41.9% with a single dose and 35.5% to 52.6% with two doses, all without serious adverse events[83]. In the ORION-10 and -11 trials, two pivotal phase-III clinical trials, inclisiran reduced LDL levels by 52.3% (ORION-10) and 49.9% (ORION-11) in patients with ASCVD who were already on maximum statin monotherapy[84,85]. A pooled analysis of ORION-9, -10, and -11 confirmed that 61.5% of inclisiran recipients achieved a reduction in LDL cholesterol of 50% or more, in contrast to only 2.2% of patients taking a placebo by 15 months. Additionally, there were significant reductions in ApoB, lipoprotein a [Lp(a)], triglyceride levels, and most importantly, the incidence of MACE[86].

ATP citrate lyase inhibitors

Beyond PCSK9, another crucial enzyme in cholesterol synthesis, ATP citrate lyase (ACL), has come into focus. In the United States, bempedoic acid, an inhibitor of ACL, has received approval for use as an adjunctive therapy to lower LDL cholesterol levels in patients with ASCVD who do not achieve their target LDL goals with statins. It has also gained approval as a primary prevention method for patients with FH[87].

The effectiveness of bempedoic acid as a lipid-lowering treatment has been recently revealed, particularly for patients who are intolerant to statins. The CLEAR trial, a large-scale study, demonstrated that bempedoic acid leads to a more substantial reduction in LDL cholesterol levels compared to placebo at both 6- (21.7% *vs.* 0.6%) and 60-month intervals (26.1% *vs.* 10.6%). Additionally, this study indicated a significant reduction in MACE when comparing the effects of bempedoic acid to placebo (11.7% *vs.* 13.3%). It is worth noting that bempedoic acid is linked to a lower incidence of myositis, making it a viable treatment alternative for patients who cannot tolerate this adverse statin effect[88].

Eicosapentaenoic Acid and Icosapent Ethyl

Icosapent ethyl is a purified derivative of eicosapentaenoic acid (EPA), which has been studied as a treatment for reducing cardiovascular risk in individuals with hypertriglyceridemia. Two multicenter,

randomized clinical trials have shown that IPE effectively lowers triglyceride levels, although these studies did not analyze cardiovascular outcomes[89].

The REDUCE-IT study aimed to assess the ability of IPE to reduce cardiovascular risk in a patient population with established risk factors who were already taking statins. Results from this study demonstrated that IPE reduced the risk of MACE by 25% compared to placebo[24]. Furthermore, the EVAPORATE study investigated whether the addition of IPE in patients with hypertriglyceridemia could lead to a reduction in the volume of coronary atheromatous plaques. These patients were already on statin monotherapy and observing dietary modifications. Its results showed a significant decrease in the volume of low attenuation plaques in the group receiving IPE therapy after 18 months of the study[90]. It has been suggested that EPA and IPE may achieve this through reduction of serum triglycerides, antiplatelet effects, anti-inflammatory and antioxidant properties, lipid membrane stabilization and inhibition of lipid oxidation[91]. IPE may also play a role in lowering remnant lipoproteins (RLP), which are highly atherogenic. The ANCHOR and MARINE studies provided evidence of IPE's efficacy in decreasing RLP levels by up to 30% compared to placebo[89].

Other therapies

Fibrates

Fibrates function by stimulating the uptake of cellular fatty acids by enhancing their conversion into acyl-CoA derivatives and subsequent catabolism through the beta-oxidation pathways. This process leads to a decrease in the production of VLDL and a reduction in the synthesis of triglycerides[92]. An extensive meta-analysis involving patients receiving treatment with fibrates indicated a decreased risk of MACE compared to placebo. However, the absolute benefits of fibrate therapy in the context of primary prevention were relatively modest[93].

Bile acid sequestrants (cholestyramine and colestipol)

Bile acid sequestrants function by capturing bile acids within the intestine, which disrupts their enterohepatic circulation, prevents their resorption, and increases their excretion in the feces. Furthermore, the reduction in the amount of bile acids transported back to the liver triggers the upregulation of hepatic cholesterol cytochrome CYP7A1. This, in turn, promotes the conversion of cholesterol into bile acids, further decreasing intrahepatic cholesterol. A meta-analysis focusing on bile acid sequestrants has revealed that these agents may serve as a complementary therapy with LDL-lowering benefits, especially in patients who cannot tolerate high-dose statins[94].

CETP inhibitors

Cholesterol ester transfer protein (CETP) is another protein involved in the transportation and formation of LDL. Its role is to transfer cholesterol esters (CE) from HDL to both VLDL and LDL. Inhibitors targeting CETP have been proven to markedly decrease LDL while increasing HDL[95].

However, the application of CETP inhibitors at present is limited due to their inadequate efficacy and safety concerns. More recently, in a phase-II trial, obicetrapib, used as an adjunct to high-intensity statins, displayed a significant reduction in LDL and non-HDL cholesterol levels with an acceptable safety profile[96]. A phase-III trial of obicetrapib is currently underway to assess its effectiveness and safety in individuals with heterozygous FH and ASCVD.

Mipomersen and lomitapide

Mipomersen and lomitapide have received approval for the treatment of FH[97,98]. Mipomersen, a second-generation antisense oligonucleotide, is complementary to human ApoB-100 mRNA. Administered subcutaneously, mipomersen operates primarily in the liver by binding to ApoB-100 mRNA. This mRNA binding leads to the inhibition of protein translation, resulting in reduced production of LDL, VLDL, and Lp(a)[99]. An analysis conducted post-hoc from three randomized clinical trials indicated a potential reduction in MACE in FH patients, which coincided with a significant decrease in LDL levels[100].

On the other hand, lomitapide acts as a microsomal triglyceride transfer protein inhibitor, impeding the formation of lipoproteins containing apoB in both the liver and intestines. Clinical investigations have indicated that lomitapide can reduce LDL levels ranging from 35% to 88%[101-104]. While the prescription of lomitapide is constrained by gastrointestinal side effects, including the development of hepatic steatosis, it is generally better tolerated than mipomersen, especially due to the absence of injection site reactions[98]. In a multicenter, retrospective, observational study, the utilization of lomitapide in FH patients was linked to a three-fold reduction in the occurrence of MACE, although this difference did not attain statistical significance[105]. Mipomersen and lomitapide are specifically reserved for patients who have FH and uncontrolled LDL despite statin therapy.

GUIDELINES (ACC/AHA AND ESC)

The 2018 ACC/AHA Guideline on the Management of Blood Cholesterol recommends high-intensity statins, capable of reducing LDL levels by 50% or more, in individuals with ASCVD who are 75 years old or younger and not at very high risk. If statin therapy fails to reach a 50% reduction in LDL, additional lipid-lowering therapy, such as ezemibe, can be used. For those over the age of 75, the decision is based on a careful assessment that considers the potential for reducing ASCVD risk, the patient's frailty, preferences, and potential adverse effects. Depending on this evaluation, either moderate- or high-intensity statins may be prescribed. Patients with ASCVD at very high risk should be prescribed high-intensity statins regardless of their age, and ezetimibe and PCSK9 inhibitors can be added to the statin regimen[9]. In the United States, alirocumab and evolocumab, and inclisiran have been approved by the FDA for use[106].

On the other hand, the 2019 ESC/EAS Guidelines for the Management of Dyslipidemias propose targeting an LDL level of 55 mg/dL or lower, as well as achieving a reduction of greater than 50% from baseline for patients at very high risk, including those with established ASCVD (previous ACS, stable angina, coronary revascularization) who require secondary prevention[11]. An even more stringent target of less than 40 mg/dL is recommended for individuals who have experienced recurrent cardiovascular events within two years[45]. In ACS patients, it is recommended to immediately start high-intensity statins regardless of initial LDL-C level and follow up within 4-6 weeks. If the LDL-C goal is not achieved, ezetimibe and PCSK9 inhibitors should be added sequentially. The latest NCEP III and ACC/AHA guidelines advocate for an LDL target of less than 70 mg/dL for individuals with diagnosed CAD or its equivalents[107].

PRACTICAL APPROACH

For patients undergoing PCI, it is advisable to consider pretreatment or a loading dose of high-intensity statins, particularly in elective cases or in those presenting with UA or NSTEMI. Even in patients with STEMI, there can be potential benefits from a loading dose of high-intensity statins. High-intensity statin therapy should be maintained after the procedure unless there are contraindications. Since a significant number of patients do not achieve their target LDL levels with statin monotherapy, a sequential approach involving the addition of ezetimibe, followed by PCSK9 inhibitors, is recommended[4]. Recent studies indicate that the initial combination therapy of statins with ezetimibe or statins with ezetimibe and PCSK9

inhibitors can be advantageous for very high-risk patient groups, as the cardiovascular benefits appear to be independent of the specific lipid-lowering mechanism[108,109].

In cases where statin intolerance is observed, ACL inhibitors like bempedoic acid can be considered. If PCSK9 inhibitors are indicated but self-injection is not well-tolerated, inclisiran can serve as an alternative. For patients with familial hypercholesterolemia, lomitapide or mipomersen may be considered as treatment options in addition to PCSK9 inhibitors.

For individuals aged over 75 who have undergone PCI but are not considered at high risk for ASCVD, it is appropriate to begin treatment with moderate-intensity statins. If the LDL cholesterol levels do not reach the target goal with this regimen, the addition of ezetimibe can be considered. In individuals who are high-risk ASCVD patients and less than 75 years old, the preferred approach is to initiate high-intensity statin therapy. If patients experience intolerance to high-intensity statins, a regimen involving moderate- or low-intensity statins, coupled with ezetimibe, can be employed.

In both of these patient groups, the inclusion of bempedoic acid can be considered if the desired LDL cholesterol target is not attained. For patients with triglyceride levels exceeding 135 mg, icosapent ethyl may be a suitable option.

Lipid-lowering medications often interact with other drugs. Statins rely on the cytochrome-p (CYP) 450 system for their metabolism, as well as organic anion transporting polypeptide (OATP), breast cancer resistance protein (BCRP), or P-glycoproteins. Inhibitors of the CYP3A4 system (such as azole antifungals and protease inhibitors) pose an elevated risk of statin-related side effects, particularly for atorvastatin, lovastatin, and simvastatin. Calcium channel blockers (like amlodipine, verapamil, and diltiazem) moderately inhibit these enzymes and should be used with caution[110]. Ticagrelor may also increase the levels of certain statins in the blood, including atorvastatin and simvastatin[111].

Pitavastatin, pravastatin, and rosuvastatin are primarily excreted such that their blood concentrations are not substantially affected by CYP3A4 inhibitors. Fluvastatin is metabolized by the CYP2C9 system, and its blood levels can be influenced by inhibitors of this enzyme. Gemfibrozil inhibits CYP2C8 and OATP1B1, so the combination of gemfibrozil and statins is not recommended due to an increased occurrence of muscle-related side effects. Fenofibrate may intensify the adverse effects of statins, making close monitoring necessary when initiating this combination.

Bempedoic acid raises the blood concentration of pravastatin and simvastatin. Consequently, doses of pravastatin exceeding 40 mg and simvastatin greater than 20 mg are not recommended in combination with bempedoic acid. When using icosapent ethyl and omega-3 acid derivatives, it is important to be aware that they may prolong bleeding time in patients taking antithrombotic agents[112].

Perspectives

Current guidelines for LLT primarily rely on data from large-scale randomized controlled trials involving patients who had CAD and received statin therapy. However, there is still a notable absence of data that would help determine whether there is a lower limit for the desired LDL cholesterol level, below which the benefits of LLT become less apparent. Future research is also necessary to investigate the advantages of non-statin therapies in terms of long-term cardiovascular outcomes and specific patient populations, such as those with advanced chronic kidney disease (CKD) or end-stage renal disease (ESRD), individuals with chronic inflammatory conditions, recipients of organ transplants, older patients (aged 75 and above), and

pregnant patients. Moreover, there is a need to address the optimal timing for initiating LLT or introducing non-statin therapies in patients who have undergone PCI.

CONCLUSION

Lipid-lowering medications have shown their effectiveness in decreasing mortality rates among patients with diverse initial cholesterol levels and individuals who have pre-existing CAD and underwent PCI. While statins are the fundamental component of this treatment, there is evidence supporting the use of ezetimibe, PCSK9 inhibitors, and ACL inhibitors as supplementary treatments to lower LDL cholesterol and the occurrence of MACE. In patients requiring or who have undergone PCI, recognizing the importance of statin, as well as integrating non-statin lipid-lowering agents, is essential for the proper implementation of lipid-lowering therapy to decrease future cardiovascular disease risk in these high-risk populations.

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Authors' contributions

Conceptualization, design, supervision, review, and revision of the manuscript: Mehran R
Manuscript drafting and revision: Godfrey K, Patnaik S, Kim CJ

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Conflict of interest

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Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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