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Role of Lipid-Lowering Therapy in Low-Density Lipoprotein Cholesterol Goal Attainment: Focus on Patients With Acute Coronary Syndrome

Qinqin Wang, MD and Chun Liang, MD

Abstract: Dyslipidemia is a major risk factor for cardiovascular (CV) disease, which is the leading cause of death globally. Acute coronary syndrome (ACS) is a common cause of death, accounting for nearly half of the global burden of CV mortality. Epidemiologic studies have identified low-density lipoprotein cholesterol (LDL-C) as an independent CV risk factor, and this is now the primary target for initiating and adjusting lipid-lowering therapies in most current guidelines. Evidence from pivotal studies supports the use of high-intensity statin therapy and a lower level for optimal LDL-C in secondary prevention of atherosclerotic CV disease, especially in patients with ACS undergoing percutaneous coronary intervention. However, current research has identified a gap between the target LDL-C goal attainment and target LDL-C levels recommended by the guidelines. Statins have proven benefits in the management of CV disease and are the cornerstone of lipid-lowering management in patients with ACS. Recent randomized controlled trials have also demonstrated the benefits of cholesterol absorption inhibitors and proprotein convertase subtilisin/kexin type 9 inhibitors. This review summarizes the current evidence for LDL-lowering therapy in patients with ACS, with an emphasis on the importance of LDL-C goal attainment, rapid LDL-C lowering, and duration of LDL-C–lowering therapy.

Key Words: acute coronary syndrome, dyslipidemia, low-density lipoprotein cholesterol, statins

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death globally, accounting for 31.4% of deaths in 2012.[1] Dyslipidemia is a widespread condition and is recognized as a major risk factor for CVD. Epidemiologic studies have identified low-density lipoprotein cholesterol (LDL-C) as an independent predictor of atherosclerotic CVD (ASCVD) and the primary target for the management of dyslipidemia.[1] Furthermore, evidence from genetic and clinical studies has also identified LDL-C as a causal factor in the pathophysiology of ASCVD.[2]

In the Asia-Pacific region, acute coronary syndrome (ACS) is a common cause of death, accounting for nearly half of the global burden of cardiovascular (CV) mortality.[3] Studies have demonstrated that intensive statin therapy can reduce the incidence of major adverse CV events (MACE) in patients with ACS.[4–7] Recent large trials of proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors have shown that substantial LDL-C lowering could further reduce the ASCVD risk in very high-risk patients.[8,9] Based on this recent evidence, current guidelines on the management of dyslipidemia recommend a lower LDL-C treatment goal in secondary prevention.[10–14] However, there is a significant gap between these recommendations and the current situation for LDL-C goal attainment. In the management of patients with ACS, including those undergoing percutaneous coronary intervention (PCI), it is necessary to rapidly lower LDL-C levels to treatment target and improve patient adherence to therapy. This review will discuss the clinical significance of LDL-C–lowering therapy in patients with ACS and consider current evidence for different treatment choices.

Epidemiology of Dyslipidemia

The disease burden of dyslipidemia is very high in terms of mortality, morbidity, and medical costs. According to estimates by the World Health Organization, dyslipidemia is associated with more than half the global cases of ischemic heart disease and more than 4 million deaths annually.[15] In 2008, the prevalence of dyslipidemia was 30.3% in South-East Asia and 36.7% in the Western Pacific, which was much lower than the rate in Europe (53.7%) and the United States (47.7%).[16] However, although cholesterol levels declined in many economically developed countries between 1980 and 2008, which has led to a reduction in coronary heart disease (CHD) mortality, they have increased in low- and middle-income countries, including China.[17] The prevalence of dyslipidemia, especially hypercholesteremia, has increased substantially over the past decade in China.[16,18,19] A recent meta-analysis of 38 observational studies found a 41.49% overall pooled prevalence of dyslipidemia in Chinese adults.[20] A total of 308 million people (31.5% of the

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From the Department of Cardiology, Changzheng Hospital, Naval Military Medical University, Shanghai, People's Republic of China.
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Reprints: Chun Liang, MD, Department of Cardiology, Shanghai Changzheng Hospital, Naval Military Medical University, No. 415 Fengyang Road, Shanghai 200003, People's Republic of China (e-mail: chunliangliang@126.com).

Chinese population) older than 20 years have borderline high or high total cholesterol, whereas 20.4% have borderline high, high, or very high LDL-C.[18]

Clinical Significance of Lowering LDL-C in Secondary Prevention

LDL-C is now well accepted as a major risk marker for ASCVD. Continuously raised LDL-C levels have been directly associated with progression from early-stage fatty streaks to advanced stage lipid-rich plaques.[1] In the Cooper Center Longitudinal Study, LDL-C of 160–189 mg/dL was associated with a 2.2-fold higher risk of CHD mortality in patients with low 10-year ASCVD risk, compared to those with LDL-C <100 mg/dL.[21] The Atherosclerosis Risk in Communities study found that the risk of an incident CHD event increased by approximately 40% for every 1 mmol/L (approximately 39 mg/dL) incremental increase in LDL-C.[22]

In major international guidelines, LDL-C is the primary target for initiating and adjusting lipid-lowering interventions.[11,23] Over the past few decades, research has focused on LDL-C–lowering therapy and its benefits on CV outcomes in secondary prevention. The Scandinavian Simvastatin Survival Study (4S study) found that simvastatin could significantly reduce coronary death by 42% in CHD patients with hypercholesterolemia.[24] Several large randomized controlled trials (RCTs) have since been conducted to demonstrate the benefits of statin therapy in patients with CHD. The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study showed that pravastatin could reduce CHD death by 24% in patients with previous myocardial infarction (MI) or unstable angina (UA) and hypercholesterolemia.[25] In 2005, the Treating to New Targets (TNT) study demonstrated that, compared with atorvastatin 10 mg per day, high-intensity statin therapy (atorvastatin 80 mg per day) provided significant clinical benefits in patients with CHD.[26]

More evidence has now emerged to support the use of high-intensity LDL-C–lowering therapy. Recent studies have shown that more intensive treatment regimens achieve a greater reduction in LDL-C levels and better clinical outcomes. A post hoc analysis of the TNT study found a significant reduction in the risk of MACE with descending achieved levels of on-treatment LDL-C. All-cause mortality was lowest with the lowest continuing on-treatment LDL-C level, and CV death was also reduced with a lower on-treatment LDL-C level.[27] Results from pivotal trials are consistent with "the lower, the better" approach to lowering LDL-C in patients with ASCVD.[13] A Cholesterol Treatment Trialists' meta-analysis showed that reducing LDL-C by 1 mmol/L results in a 10% relative reduction in all-cause mortality.[6] Findings from recent studies of combination treatments with ezetimibe and PCSK-9 inhibitors in patients with ASCVD also support a more intensive LDL-C target[8,9] and have led to changes in recommendations by major guidelines.

An Overview of Treatment Guidelines

Treatment guidelines for the management of dyslipidemia recommend ASCVD risk assessment as the basis for treatment strategy.[10–14,28] Patients with ACS are considered as very high risk for ASCVD, and the guidelines recommend high-intensity statin therapy as initial treatment and then combination treatments if LDL-C goals are not met despite maximum tolerated statin dose.[10,11]

The American College of Cardiology/ American Heart Association (ACC/AHA) Cholesterol Clinical Practice Guidelines

For patients with clinical ASCVD, the ACC/AHA guidelines (2018) recommend high-intensity statin therapy, or maximum tolerated statin therapy, to reduce the LDL-C level by at least 50%. For very high-risk ASCVD patients, the guidelines recommend aiming for an LDL-C threshold of 70 mg/dL (1.8 mmol/L) and to consider adding nonstatin therapy.[11]

For patients with ACS, the ACC/AHA Guideline for the Management of Patients with Non-ST-Elevation ACS (NSTE-ACS) (2014) recommends initiating, or continuing, high-intensity statin therapy in all patients with NSTE-ACS. The guideline emphasizes the increased benefit of high-intensity statins in reducing CV events in these very high-risk patients, as well as the importance of early introduction of this approach, as it can promote improved compliance with this regimen.[29]

The European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS) Guidelines for the Management of Dyslipidaemias

In 2016, the ESC/EAS guidelines recommended early initiation of high-intensity statin therapy in very high-risk patients, aiming to reach LDL-C goal of <1.8 mmol/L or LDL-C reduction of at least 50%.[23] Based on the studies of ezetimibe and PCSK-9 inhibitors, the updated 2019 ESC/EAS guidelines recommend an LDL-C reduction of at least 50% from baseline and a lower target LDL-C goal <1.4 mmol/L (55 mg/dL) for secondary prevention in very high-risk patients, including those with ACS. To achieve the target, high-intensity statin therapy should be initiated in all statin-naive ACS patients as early as possible, regardless of baseline LDL-C levels. Furthermore, for patients with ASCVD who experience a second vascular event within 2 years while on maximum tolerated statin-based therapy, an LDL-C level <40 mg/dL may be considered. Routine pretreatment or loading with a high-intensity statin is recommended in patients with ACS undergoing PCI.[10]

A comparison of the 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias and the 2018 ACC/AHA Cholesterol Clinical Practice Guidelines is provided in Table 1.

Asian Lipid-Lowering Guidelines

The evidence behind the recommendations in major international guidelines is generally based on the data from Western populations, but their applicability to Asian populations is largely untested.[30] Current evidence suggests that Asian populations may have a stronger response to statins than Whites, and that the incidence of adverse events could

TABLE 1. A Comparison of the ESC/EAS (2019) Guidelines for the Management of Dyslipidaemias and the ACC/AHA (2018) Cholesterol Clinical Practice Guidelines: Recommendations for Very High-Risk Patients

Guideline	Target LDL-C Goal	Recommended Statin Therapy	Other Treatment Recommendations	Monitoring
ESC/EAS (2019)[10]	≥50% reduction from baseline and <1.4 mmol/L (55 mg/dL) <40 mg/dL may be considered for patients with ASCVD who experience a second vascular event within 2 yr while on maximum tolerated statin-based therapy	High-intensity statin therapy should be initiated early (during the first 1–4 days of hospitalization for the index ACS) In all patients with ACS without contraindication or definite history of intolerance, it is recommended to initiate or continue high-dose statin as early as possible, regardless of initial LDL-C levels Routine pretreatment or loading (on a background of chronic therapy) with a high-dose statin should be considered in patients undergoing PCI for an ACS or elective PCI	If the LDL-C target is not achieved after 4–6 weeks despite maximum tolerated statin therapy, combination with ezetimibe is recommended If the LDL-C target is not achieved after 4–6 weeks despite maximum tolerated statin therapy and ezetimibe, addition of a PCSK-9 inhibitor is recommended For patients who present with an ACS and whose LDL-C levels are not at goal despite already taking a maximally tolerated statin dose and ezetimibe, adding a PCSK-9 inhibitor early after the event should be considered	Lipids should be re-evaluated 4–6 wk after ACS to determine whether a reduction of at least 50% from baseline and goal levels <1.4 mmol/L have been achieved Safety issues need to be assessed at this time, and statin treatment doses adapted accordingly
ACC/AHA (2018)[11]	In clinical ASCVD: reduce LDL-C levels by ≥50% In very high-risk ASCVD: <70 mg/dL (1.8 mmol/L)	High-intensity statin therapy or maximum tolerated statin therapy is recommended	In very high-risk ASCVD: consider adding ezetimibe to maximally tolerated statin therapy when LDL-C remains ≥70 mg/dL (≥1.8 mmol/L) and adding a PCSK-9 inhibitor if LDL-C ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy	Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes Repeat lipid measurement should be performed 4–12 weeks after statin initiation or dose adjustment, and repeated every 3–12 months, as needed

ACC/AHA, American College of Cardiology/American Heart Association; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol; PCI. percutaneous coronary intervention; PCSK-9, proprotein convertase subtilisin/kexin type 9.

be higher in Asian patients.[30–32] Rosuvastatin plasma levels have been found to be 2-fold higher in East Asians than those in Whites and have resulted in a greater LDL-C reduction, consistent with ethnic differences observed in the pharmacokinetics of this agent.[31,32] Although findings from a large meta-analysis of 181 RCTs with 256,827 patients support the evidence for a dose–response relationship in lowering LDL-C and total cholesterol,[33] the CHILLAS trial found no significant difference in the reduction of LDL-C levels between high- and moderate-intensity statin therapy in Chinese patients with acute MI (AMI) or UA and a low baseline LDL-C level (mean 2.7 mmol/L). In addition, there was no significant difference in the primary end points (cardiac death, nonfatal AMI, revascularization, ischemic stroke and UA, or severe heart failure) between the groups. The authors concluded that, for ACS patients with a low LDL-C, the incremental reduction of 6.4% achieved by double-dose statin therapy did not bring about significant effectiveness.[34] Therefore, treatment with lower statin doses in selected Asian patients could be sufficient to attain the LDL-C target level.

Current guidelines from East Asian countries, including the Chinese guidelines for the management of dyslipidemia (2016), recommend a target LDL-C level of <70 mg/dL in very high-risk patients.[28,35–37] Based on the trials of PCSK-9 inhibitors, the China Cholesterol Education Program Expert Advice for the Management of Dyslipidemia recommends a target LDL-C level of 1.4 mmol/L in "super high-risk" patients. These include patients with established ASCVD as well as additional risk factors (recurrent ASCVD, multivessel coronary disease, recent ACS, coronary/intracranial or peripheral atherosclerosis disease, LDL-C ≥4.9 mmol/L, or diabetes).[38] In line with the observed differences in response to statins in East Asian populations, Chinese guidelines recommend initiating moderate-intensity statin therapy.[28] Table 2 provides an overview of recommendations from current East Asian guidelines[28,35–37] for secondary prevention in patients at very high risk of CVD.

The Importance of LDL-C Management in Patients With ACS

LDL-C Goal Attainment

Current guidelines emphasize the importance of LDL-C reduction in patients with ACS. A Cholesterol Treatment Trialists' meta-analysis demonstrated that for patients with previous CHD, the relative reduction for major vascular events per 1 mmol/L reduction in LDL-C was 0.79 (95% confidence interval, 0.76–0.82).[6] In another meta-analysis comprising 49 trials

TABLE 2. An Overview of Current East Asian Guidelines for Secondary Prevention in Patients at Very High Risk of CVD

Guideline	Target LDL-C Goal	Recommended Statin Therapy	Other Treatment Recommendations
Chinese guidelines (2016)[28]	LDL-C target <70 mg/dL or lowering by ≥50% if baseline LDL-C is high and target cannot be achieved, and by ~30% if baseline LDL-C <70 mg/dL	Start with medium-intensity statin therapy	Consider a combination of other lipid-lowering drugs if target LDL-C cannot be achieved
Korean guidelines (2018)[36]	LDL-C target <70 mg/dL or lowering by >50% of baseline if target not achieved	Statin administration should be considered to meet the LDL-C target In acute MI, statin should be immediately administered regardless of baseline LDL-C	Combination with ezetimibe should be considered if LDL-C target is not achieved even after using maximum tolerable dose of statin PCSK-9 inhibitors may be considered for concurrent use if LDL-C target is not achieved even after using statin alone or with ezetimibe
Taiwan guidelines (2017)[37]	LDL-C target <70 mg/dL in ACS, CAD, and PAD LDL-C target <55 mg/dL can be considered in ACS + DM	Statins are for first-line therapy, and moderate- or high-intensity statins are preferred	Ezetimibe alone can be considered in patients who have statin contraindications or intolerance Statin or statin/ezetimibe should be used for all patients with ACS if there is no contraindication Statin or statin/ezetimibe therapy should be started within the first few days of hospitalization for ACS and before PCI for ACS PCSK-9 inhibitors can be added if LDL-C target is not reached with statin/ezetimibe
Japan guidelines (2017)[35]	LDL-C target <100 mg/dL in patients with a history of CAD LDL-C target <70 mg/dL in patients with FH, ACS, and DM complicated by other high-risk conditions	It is appropriate to consider statins as the first medication of choice Aggressive treatment should be initiated immediately after the disease onset	Ezetimibe, PCSK-9 inhibitor, and EPA have been proven to be effective for the prevention of ASCVD when used in combination with statins

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CVD, cardiovascular disease; DM, diabetes mellitus; EPA, eicosapentaenoic acid; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral arterial disease; PCSK-9, proprotein convertase subtilisin/kexin type 9.

and 312,175 patients, the relative reduction for major vascular events per 1 mmol/L reduction in the LDL-C level was 0.77 (95% confidence interval, 0.71–0.84; $P < 0.001$) for statins.[39] These results demonstrated that lower achieved LDL-C levels were associated with lower rates of major coronary events.

In patients with ACS, the breakthrough ODYSSEY study further showed that greater LDL-C reductions were associated with greater benefits.[9] A retrospective, cohort study in Hong Kong assessed the effect of LDL-C goal attainment (<2.6 and 1.8 mmol/L) on first MACE in 1684 patients with ACS undergoing PCI. At 1 year, 39.1% of patients attained LDL-C of <1.8 mmol/L, and 43.2% attained LDL-C of 1.8–2.6 mmol/L. Attainment of the LDL-C level of <2.6 mmol/L was significantly associated with a decreased incidence of MACE, and those with 1.8 mmol/L did not carry any incremental clinical benefits. However, patients who attained LDL-C <1.8 mmol/L had a much lower baseline LDL-C, and the absolute reduction was low.[40] This result suggested that even for those patients with low baseline LDL-C levels, achieving a greater LDL-C reduction is important for improving clinical outcomes. Findings from both RCTs and real-world data have emphasized the importance of aggressive reduction of LDL-C levels in patients with ACS.

The Importance of Rapid LDL-C Reduction

The ALPS-AMI study in patients with AMI who underwent PCI found that a rapid reduction of LDL-C levels was strongly associated with favorable outcomes. Both relative and absolute reductions in LDL-C levels at 4 and 8 weeks were significantly higher in the early reduction group. The incidence of MACE and cardiac deaths was significantly higher in the late reduction group.[41] Research has found that circulating PCSK-9 levels are associated with inflammation in ACS. The novel options of PCSK-9 inhibitors have enabled a rapid reduction of LDL-C levels to <1 mmol/L without safety issues.[8,9] These findings may suggest that early treatment with PCSK-9 inhibitors, leading to a rapid reduction of LDL-C levels, could result in greater clinical benefits.[42] However, current ESC/EAS guidelines recommend re-evaluating LDL-C levels 4–6 weeks after ACS to decide whether to initiate ezetimibe or PCSK-9 inhibitors.[10] The benefit of achieving a large or rapid reduction of LDL-C levels after ACS is still unclear.[41]

Duration of Statin Therapy

Most lipid-lowering treatment (LLT) trials are limited in duration. However, as the disease occurs over a long period

of time and treatment is lifelong, the extent of the lifetime benefit of LLT has been emphasized. Several secondary prevention trials have conducted long-term follow-up of mortality and morbidity outcomes (11-year follow-up in the Heart Protection Study; 10.4-year extended observation period in 4S; 8-year observation period in LIPID) and have shown that relative risk reduction persists beyond the end of the formal double-blind phase.[43–46] The LIPID trial initially compared pravastatin and placebo in over 9000 patients with CHD over 6 years[25]; in 2016, the investigators published 16 years of follow-up data from this study. During the extended follow-up, 85% of patients in the pravastatin group and 84% in the placebo group underwent statin therapy. The pravastatin group maintained a significantly lower risk for CHD, CV, and all-cause mortality.[47]

A meta-analysis that included 58 clinical trials and 148,321 patients examined the reduction in risk of ischemic heart disease by duration of statin treatment. This study demonstrated that the ischemic heart disease risk reduction per 1.0 mmol/L reduction in the LDL-C level was 11% in the first year and 36% in the sixth and subsequent years.[48] Results of this meta-analysis suggested that longer duration of statin treatment was associated with greater reductions in CVD risk. Although extended follow-up studies of statin therapy in patients with ACS are limited, previous secondary prevention trials have demonstrated that longer duration of statin therapy may bring consistent benefits.[43–48]

LDL-C–Lowering Strategies in Patients With ACS

Statins

Benefits of statins in secondary prevention are well established.[1] Several large RCTs of statins in secondary prevention have shown that, when compared with placebo, statin therapy significantly reduced the incidence of MACE.[24,26,49–52] Most evidence demonstrates that the major benefit of statin therapy is due to lowering of LDL-C.[13]

Evidence from the PROVE IT-TIMI 22 trial suggests that intensive statin therapy significantly reduces the incidence of MACE in patients with ACS. This study found that, compared with pravastatin 40 mg per day, atorvastatin 80 mg per day reduced the first occurrence of primary end points (death, MI, UA requiring hospitalization, stroke, and revascularization ≥30 days) by 16% and subsequent events by 19%.[49,53]

The TNT trial investigators found a significant reduction in the incidence of MACE with high-dose atorvastatin in patients with stable CHD, with the mean on-treatment LDL-C level of 77 mg/dL compared with 101 mg/dL with a lower dose.[26] In a PROVE IT-TIMI 22 subgroup analysis, patients who achieved LDL-C <40 and 40–60 mg/dL experienced fewer major cardiac events.[54] Based on current evidence, physicians should consider using high-intensity statins in the management of patients with ACS to achieve a greater LDL-C reduction. According to international guidelines on the management of dyslipidemia, rosuvastatin 20–40 mg and atorvastatin 40–80 mg are considered as high-intensity statins.[10,11] A summary of findings from pivotal trials[26,49,55,56] assessing the impact of high-intensity statin therapy on LDL-C and CV outcomes is presented in Table 3. The VOYAGER meta-analysis compared the percentage change of LDL-C with different doses of atorvastatin, rosuvastatin, and simvastatin. This analysis included results of 15,800 patients with hypertriglyceridemia from the VOYAGER database and found that rosuvastatin 10–40 mg achieved significantly greater LDL-C reductions than equal or double doses of atorvastatin and simvastatin. A significant individual variability in response to statin treatment was observed at all doses of these three statins.[57]

Pretreatment or Loading Dose of Statin Therapy Before PCI

Several small studies in ACS have been conducted in patients with non-ST-elevation MI (NSTEMI) and demonstrated that pre-PCI statin pretreatment reduced the incidence of MACE and/or post-PCI elevation in levels of myocardial injury and inflammatory markers.[58–67] A summary of trials[58–70] of statin pretreatment in patients with ACS undergoing PCI is provided in Table 4. Although the precise mechanism of inhibition of elevated myocardial and inflammatory markers by statins is not fully understood, it is believed that it may be due to their pleiotropic effects, especially to vascular inflammation.[61]

Vascular inflammation plays a major pathogenic role in ACS, and its extent is associated with adverse late clinical outcomes in both ACS and PCI. In patients with NSTE-ACS, elevated levels of C-reactive protein (CRP) have been correlated with an increased incidence of death or nonfatal MI up to 6 months after PCI. Furthermore, markedly increased CRP level before early revascularization for NSTE-ACS has been identified as a predictor of mortality to 5 years of follow-up.[71]

The 2019 ESC/EAS guidelines on the management of dyslipidemia recommended that routine pretreatment or loading (on a background of chronic therapy) with a high-dose statin should be considered in patients undergoing PCI for an ACS or elective PCI.[10] In a meta-analysis of 13 randomized studies including 3341 patients, pretreatment with a high-dose statin (statin-naive patients, 11 studies) or a high-dose statin loading dose reduced the risk of MACE by 44% for both periprocedural MI and MACE at 30 days.[72] However, most of these studies included patients with stable angina (SA) and elective PCI. In the ISCAP trial, researchers compared the intensive statin treatment with usual care in 1202 patients with SA or NSTEMI who underwent PCI. The incidence of 30-day MACE (cardiac death, MI, or unexpected target vessel revascularization) was similar between the two groups.[73] This trial indicated that serial intensive statin regimens did not improve clinical outcomes in Chinese patients undergoing elective PCI. Similarly, the recent SECURE-PCI trial that included 4191 patients with ACS and planned invasive management in Brazil examined whether periprocedural statin loading doses could decrease the incidence of 30-day MACE. At 30 days, the incidence of MACE was 6.2% in the loading dose group and 7.1% in the placebo group, without statistical significance.[74] Thus, findings of these two large trials do not support routine use of statin loading doses in patients with ACS undergoing PCI.

TABLE 3. Summary of Trials Comparing the Impact of High-Intensity vs. Standard Statin Therapy on LDL-C and CV Outcomes in Secondary Prevention

Study	Follow-up (yr)	Patients (n)	Population	Baseline LDL-C (mg/dL)	Statin(s)/Dose (mg)	Primary Endpoint(s)	LDL-C Reduction (Change Relative to the Comparator Arm)	MACE Rate
PROVE-IT-TIMI 22[49]	2.0 (mean)	4162	Patients with ACS within previous 10 d	106 (median)	Atorvastatin 80 vs. pravastatin 40	Death, MI, stroke, UA with rehospitalization, or revascularization >30 days after index ACS event	33.0 mg/dL (31%)	Atorvastatin group 22.4% vs. 26.3% RR = 16% with atorvastatin (P = 0.005)
TNT[26]	4.9 (median)	10,001	Patients with clinically evident CHD	152 (mean)	Atorvastatin 80 vs. atorvastatin 10	Death from CHD, nonfatal MI, resuscitation after cardiac arrest, or stroke	24 mg/dL (16%)	Atorvastatin 80 group 8.7% vs. atorvastatin 10 group 10.9% RR = 22% with atorvastatin 80 (P <0.001)
IDEAL[55]	4.8 (median)	8888	Patients with a history of AMI	122 (mean)	Atorvastatin 80 vs. simvastatin 20	Coronary death, nonfatal AMI, or cardiac arrest with resuscitation	23 mg/dL (19%)	Atorvastatin group 9.3% vs. simvastatin 10.4% RR = 11% with atorvastatin (P = 0.07)
A–Z[56]	2.0 (median)	4497	Patients with ACS	112 (median)	Simvastatin 40 for 1 month and then simvastatin 80 vs. control group (placebo for 1 month and then simvastatin 20)	A composite of CV death, nonfatal MI, readmission for ACS, and stroke	15 mg/dL (13%)	Simvastatin group 14.4% vs. control group 16.7% (P = 0.14) RR = 11% with simvastatin only (P = 0.14)

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CHD, coronary heart disease; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MI, myocardial infarction; RR, relative risk.

Based on these results, which have shown inconsistent benefits of routine statin loading doses, continuous high-intensity statin therapy may be sufficient to achieve improved clinical outcomes in patients with ACS undergoing PCI.

Ezetimibe

Until the IMPROVE-IT trial, the clinical value of ezetimibe was unclear. This study included 18,144 patients with ACS ≤10 days and a mean baseline LDL-C level of 2.4 mmol/L. The combination of simvastatin and ezetimibe lowered patients' LDL-C levels more than simvastatin alone (mean LDL-C at 1 year: 1.4 vs. 1.8 mmol/L) and significantly reduced the primary end point first event (CV death, MI, rehospitalization for UA, coronary revascularization, or stroke) by 6.4% (34.7% vs. 32.7%; P = 0.016).[75] The benefits were more evident in patients with diabetes mellitus and those aged 75 years or older.[76]

Based on the IMPROVE-IT trial results, ezetimibe is recommended in combination with statins for patients whose LDL-C levels are still not at goal despite maximum tolerated statin therapy and further intensifying treatment with the addition of a PCSK-9 inhibitor.[10,11,14]

PCSK-9 Inhibitors

Two recent key placebo-controlled, randomized trials with PCSK-9 inhibitors added to maximum statin therapy have found a 15% relative risk reduction in the composite end point (CHD death, MI, stroke, and UA requiring hospitalization).[10] In the FOURIER study involving 27,564 patients with ASCVD and LDL-C ≥70 mg/dL, the addition of evolucumab to patients' statin therapy resulted in a 59% reduction in LDL-C levels and a significant reduction in the primary end point (9.8% vs. 11.3%; hazard ratio = 0.85; P < 0.001).[8] The ODYSSEY trial of alirocumab in 18,924 patients with ACS on statin therapy (atorvastatin 40–80 mg or rosuvastatin 20–40 mg) also found a significant reduction in the composite primary end point (9.5% vs. 11.1%; hazard ratio = 0.85; P < 0.001), with the highest absolute benefit observed in patients with a baseline LDL-C of ≥100 mg/dL. In the intention-to-treat analysis, mean LDL-C in the alirocumab group at 4, 12, and 48 months was lower than that in the placebo group (40 vs. 93 mg/dL, 48 vs. 96 mg/dL, and 66 vs. 103 mg/dL, respectively).[9]

A recent study of evolucumab as add-on treatment to high-intensity statin therapy (atorvastatin 40 mg) in 308

TABLE 4. Summary of Trials of Statin Pretreatment in Patients With ACS Undergoing PCI

Study	Objectives	Population	Patients	Intervention	Results
Chyrchel et al (2006)[58]	To assess whether short-term, high-dose statin therapy before PCI in patients with NSTE-ACS produces long-term clinical benefits	Polish patients with NSTE-ACS undergoing PCI with hs-CRP >3 mg/L	140	Atorvastatin 80 mg for 3 days pre-PCI (n = 86) vs. no statin (n = 54) before PCI, followed by atorvastatin 40 mg	MACE rate at follow-up Atorvastatin group (mean follow-up: 592 ± 360 d) 8.1% vs. no statin group (mean follow-up: 641 ± 373 d) 25.9% (P = 0.006)
ARMYDA-ACS Patti et al (2007)[59]	To investigate potential protective effects of atorvastatin in patients with ACS undergoing PCI	Patients with NSTE-ACS undergoing PCI	171	Atorvastatin 80 mg 12 h before PCI and 40 mg preprocedural dose (n = 86) vs. placebo (n = 85)	MACE rate at 30 days Atorvastatin group 5% vs. 17% (P = 0.01) RR = 88% with atorvastatin (P = 0.004) Post-PCI elevation levels of myocardial injury markers Atorvastatin group CK-MB 7% vs. 27% (P = 0.001) and cTnI 41% vs. 58% (P = 0.039)
AMERICA Hara et al (2009)[61]	To investigate the effect of preprocedural aggressive statin therapy in NSTE-ACS	Japanese patients with NSTE-ACS	37	Atorvastatin 20 mg (n = 16) vs. no statin (n = 21)	Post-PCI elevation levels of myocardial injury markers At 3 days: CK atorvastatin group 84 ± 17 IU/L vs. 180 ± 68 IU/L (P = 0.02) CK-MB atorvastatin group 3 ± 4 vs. 7 ± 3 (P = 0.07) BNP atorvastatin 3.2 ± 1.9 pg/mL vs. 7.0 ± 3.0 pg/mL (P = 0.07) Changes in LDL-C levels (mg/dL) At 2 weeks: atorvastatin group −47.5 ± 32.7 vs. −13.3 ± 27.6 (P = 0.005)
Yun et al. (2009)[60]	To study whether single high-dose statin loading is beneficial on the outcome of patients with ACS undergoing PCI	Korean patients with NSTE-ACS undergoing PCI	445	Rosuvastatin 40 mg (n = 225) or no statin (n = 220) before PCI	PMI Rosuvastatin group 5.8% vs. 11.4% (P = 0.035) Post-PCI elevation levels of myocardial injury markers CK-MB and cTnI significantly higher in the control group
Sun et al (2010)[62]	To compare the safety and efficacy of different atorvastatin LDs and dosing frequency before PCI	Chinese patients with NSTE-ACS undergoing PCI	80	Atorvastatin 80 mg (low-load) 12 h pre-PCI (n = 20) vs. atorvastatin 40 mg (mid-load) 2 h pre-PCI (n = 20) vs. atorvastatin 60 mg (high-load) 2–4 h pre-PCI (n = 20) vs. atorvastatin 40 mg at night control group (n = 20), followed by atorvastatin 40 mg at night for at least 1 mo	MACE rate at 30 days Atorvastatin 60 mg 2–4 h pre-PCI 0% vs. 40 mg 2 h pre-PCI 10% vs. 80 mg 12 h pre-PCI 25% vs. 40 mg at night (P <0.05) MACE rate increased (above normal range), cTnI increased, CK-MB increased, hs-CRP all significantly higher in the control group vs. high-load group (atorvastatin 60 mg 2–4 h pre-PCI)

TABLE 4. (*Continued*) Summary of Trials of Statin Pretreatment in Patients With ACS Undergoing PCI

Study	Objectives	Population	Patients	Intervention	Results
Yun et al. (2011)[13]	To investigate whether a single high-dose statin loading before PCI has beneficial effects on long-term clinical outcomes	Korean patients with NSTE-ACS undergoing PCI	445	Rosuvastatin 40 mg (n = 225) or no statin (n = 220) before PCI	MACE at follow-up (mean = 11 ± 3 months) Rosuvastatin group 9.8% vs. 20.5% (P = 0.002) Mean LDL-C levels and hs-CRP were not different between the groups at 1 mo and at 6 mo LDL-C goal attainment At 1 mo: rosuvastatin group 54.3% vs. 56.0% (P = 0.410) At 6 mo: rosuvastatin group 60.0% vs. 60.5% (P = 0.509)
Gao et al. (2012)[64]	To study the effect of rosuvastatin loading therapy before PCI in female patients with NSTE-ACS	Chinese female patients with NSTE-ACS undergoing PCI	117	Rosuvastatin 20 mg 12 h before angioplasty and 10 mg 2 h preprocedural (n = 59) vs. no rosuvastatin group (n = 58)	MACE rate At 3 months: rosuvastatin group 1.69% vs. 12.07% (P = 0.026) At 6 months: rosuvastatin group 3.39% vs. 17.24% (P = 0.014) Post-PCI elevation levels CK-MB: rosuvastatin group 10.17% vs. 25.86% (P = 0.027) cTni: rosuvastatin group 11.86% vs. 29.31% (P = 0.019) hs-CRP, IL-1, IL-6, and TNF-α significantly higher in the control group Post-PCI LDL-C (mmol/L) Atorvastatin 2.02 ± 0.84 vs. 2.56 ± 0.89
Wang et al (2013)[65]	To investigate whether pretreatment with rosuvastatin can reduce procedural myocardial damage and determine whether variations in postprocedural levels of hs-CRP, IL-6, and MCP-1 are influenced by rosuvastatin pretreatment	Patients with NSTE-ACS undergoing PCI	125	Rosuvastatin 20 mg 2–4 h pre-PCI (n = 62) vs. placebo (n = 63) followed by rosuvastatin 10 mg/day long term	MACE rate at 30 days Rosuvastatin group 8.1% vs. 22.2% (P <0.01) Post-PCI elevation levels of myocardial injury markers CK-MB and cTnI significantly lower in the rosuvastatin group at 6 h, 24 h, and 3 days Post-PCI elevation levels of inflammatory markers Hs-CRP and IL-6 were significantly lower in the rosuvastatin group
ALPACS Jang et al (2014)[66]	To assess the effect of pretreatment with atorvastatin on CV events	Statin-naive Chinese and Korean patients with NSTE-ACS undergoing PCI	499	Atorvastatin 80 mg 12 h pre-PCI and 40 mg 2 h post-PCI (n = 247) vs. usual care (n = 252)	MACE rate at 30 days: Atorvastatin group 15% vs. 16% (NS)

(*continued on next page*)

TABLE 4. (*Continued*) Summary of Trials of Statin Pretreatment in Patients With ACS Undergoing PCI

Study	Objectives	Population	Patients	Intervention	Results
Kim et al (2014)[68]	To investigate the effects of high-dose rosuvastatin LD before primary PCI on the infarct size	Korean patients with STEMI	475	Rosuvastatin 40 mg (n = 208) vs. no statin (n = 267)	Infarct size (assessed by SPECT) Rosuvastatin group 19.0 ± 15.9% vs. 22.9 ± 16.5% (P = 0.009) Corrected TIMI frame count Rosuvastatin group 28.2 ± 19.3 vs. 32.6 ± 21.4 (P = 0.020) MBG: rosuvastatin group 2.49 ± 0.76 vs. 2.23 ± 0.96 (P = 0.001) MACE rate at 30 days Rosuvastatin 0% vs. 1.5% (P = 0.073)
Jiao et al (2015)[67]	To assess the effect of LD rosuvastatin on Lox-1, hs-CRP, and LVEF	Elderly Chinese patients (≥70 years old) with NSTE-ACS	126	Rosuvastatin 20 mg 12 h before PCI plus second dose just before PCI (n = 62) vs. standard statin therapy (n = 64), followed by rosuvastatin 10 mg 24 h after PCI	Post-PCI elevation levels of myocardial and inflammatory markers At 24 h: the rosuvastatin LD group had significantly lower increased serum sLox-1, hs-CRP, CK-MB, and cTnI levels ($P < 0.05$) and lower sLox and hs-CRP (no significant difference) At 30 days: decreased BNP ($P < 0.05$) and increased LVEF ($P < 0.05$)
Liu et al. (2016)[69]	To test the efficacy of high-intensity statin therapy for the reduction in PMI and 1-yr MACE	Chinese patients with SA or ACS	798	Atorvastatin 80 mg before PCI and 40 mg/d thereafter for 1 yr (n = 400) vs. atorvastatin 20 mg/day for 1 yr (n = 398)	MACE rate at 1 year ACS group: Atorvastatin 80 mg 10.1% vs. atorvastatin 20 mg 16.8% (P = 0.021) SA group: Atorvastatin 80 mg 5.7% vs. atorvastatin 20 mg 7.6% (P = 0.53)
Liu et al (2018)[70]	To compare the long-term efficacy and safety of high-intensity and conventional low-intensity atorvastatin therapy in reducing LDL-C of patients with ACS undergoing PCI	Chinese patients with ACS undergoing PCI	120	Atorvastatin 80 mg pre-PCI followed by 40 mg/day for 3 months after PCI (n = 60) vs. atorvastatin 20 mg/day from the date of admission until 1 year after PCI (n = 60)	LDL-C goal attainment at week 48 85% of the high-intensity atorvastatin group vs. 96.7% achieved the target level (high-intensity group had higher baseline LDL-C levels and 8.3% had LDL-C <1.81 mmol/L) Mean percentage change in LDL-C At 4 wk: −33.6% ± 20.0% vs. −12.8% ± 19.6% ($P <$ 0.0001) At 48 wk: 47.0% ± 25.5% vs. −36.4% ± 20.2% (P = 0.0131)
SECURE-PCI Berwanger et al (2018)[74]	To determine whether periprocedural loading doses of atorvastatin decrease 30-day MACE in patients with ACS and planned invasive management	Brazilian patients with ACS undergoing PCI	4191	Atorvastatin 80 mg (n = 2087) vs. placebo (n = 2104) before and 24 h after PCI	MACE rate at 30 days Atorvastatin group 6.2% vs. 7.1% (NS)

ACS, acute coronary syndrome; BNP, brain natriuretic peptide; CK-MB, creatine kinase-myocardial band; cTnI, cardiac troponin-I; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; LD, loading dose; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MBG, myocardial blush grade; MCP, monocyte chemotactic protein; NS, not significant; NSTE, non-ST-segment elevation; PCI, percutaneous coronary intervention; PMI, periprocedural myocardial infarction; sLox-1, soluble lectin-like oxidized low-density lipoprotein receptor-1; SPECT, single-photon emission computed tomography; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; TNF, tumor necrosis factor.

patients hospitalized for ACS with elevated LDL-C levels found a significant reduction in LDL-C levels at week 8, with more than 95% of patients achieving LDL-C levels <1.8 mmol/L.[77] The combination of a PCSK-9 inhibitor and high-intensity statin treatment could increase the control rate and improve the management of LDL-C in patients with ACS.

The FOURIER and ODYSSEY studies found no observed effect on CV mortality and, in addition, FOURIER found no significant reduction in all-cause mortality. However, these studies had a relatively short follow-up and, as evidence from statin trials indicates, clinical benefits of LDL-C lowering may emerge after approximately 1 year. The 2019 ESC/EAS guidelines recommend that lipid levels should be re-evaluated 4–6 weeks after ACS to determine whether the LDL-C goal level has been achieved and whether to combine ezetimibe or PCSK-9 inhibitor therapy.[10] In previous clinical trials, the benefits of ezetimibe or a PCSK-9 inhibitor were evaluated on the base of statin therapy.[8,9,76] Combination of ezetimibe or a PCSK-9 inhibitor should be initiated after evaluation of the lipid level. However, in selected patients with ACS undergoing PCI who have a high LDL-C level, a rapid reduction of LDL-C using early combination treatment might be beneficial. In patients with ACS, the appropriate timing for adding combination treatment with ezetimibe and a PCSK-9 inhibitor needs to be further investigated.

Adherence to LLT and LDL-C Goal Attainment —Current Situation

Although adherence to LLT has improved in recent years, evidence shows that most patients receiving high-dose statins fail to reach goal LDL-C levels.[13] In the DYSIS II study, the percentage of patients with ACS on LLT increased from admission (65.2%) to 120-day follow-up (95.6%); however, only 18.9% achieved an LDL-C level of <70 mg/dL.[78] The results of the French cohort showed substantial improvement in LDL-C attainment goals compared with DYSIS[79]; however, two-thirds of patients in DYSIS II still had elevated LDL-C levels.[80] The authors concluded that their findings are broadly in agreement with the EUROASPIRE studies. Compared with the EUROASPIRE II survey, EUROASPIRE IV showed a doubling in high-intensity statin use and 20% increase in achieved LDL-C target of <1.8 mmol/L.[80] However, the EUROASPIRE IV survey found that a large majority of patients with CHD did not achieve LDL-C goal for secondary prevention.[81] In this study, only 37.6% of patients were on high-intensity statin therapy at discharge, which decreased to 32.7% at follow-up.[82] Therefore, although 85.7% of patients were on statin therapy, target LDL-C <1.8 mmol/L was achieved by only 19.3% of patients.[82] Recently, EUROASPIRE V also found less than optimal management of LDL-C in patients with established coronary disease. Between hospital discharge and the next clinical visit (median time, 1.12 years), 20.8% of patients had their LLT reduced in intensity or interrupted; almost half of the patients were on high-intensity statin therapy and 71% had LDL-C ≥70 mg/dL.[83] LDL-C goal attainment rates in major epidemiologic studies[3,78,80,81,83–86] are presented in Table 5.

Research in Chinese patients with CHD has also shown a low LDL-C goal achievement rate. In the China Cholesterol Education Program study in patients with a history of CHD, approximately 82% received statin therapy, but only 10.9% of the very high-risk patients achieved the optimal LDL-C level of <1.8 mmol/L.[31] A recent multicenter, cross-sectional study in 2034 Chinese patients with ACS within the previous 4–40 weeks who were on statins for longer than 2 weeks (74.9% of patients were on intensive statin therapy) found that 63.8% did not achieve LDL-C goal at the time of enrollment, with a mean LDL-C level of 2.460 ± 0.714 mmol/L.[87]

TABLE 5. Findings From Studies of Patients Who Achieved Target LDL-C <70 mg/dL (<1.8 mmol/L)

Study	Population	Patients (n)	Percentage of Patients With LDL-C <70 mg/dL (<1.8 mmol/L)	Timing of LDL-C Laboratory Findings
DYSIS II[78]	Patients with stable CHD or ACS	(ACS) 3867	18.9%	At hospital admission
DYSIS II (French cohort)[79]	Patients with stable CHD or ACS	(ACS) 468	16.9%	At hospital admission
DYSIS II (Hong Kong and Taiwan cohort)[2]	Patients with stable CHD or ACS	(ACS) 270	17%	At hospital admission
EUROASPIRE IV[82]	Patients with CAD who had CABG, PCI, or ACS	6648	19.3%	As per patient, interviews conducted 6–36 mo after the diagnoses of first or recurrent CAD
EUROASPIRE V[83]	Patients with CHD who had CABG, PCI, or ACS	7824	29%	As per patient, interviews conducted 6 mo to 2 yr after hospitalization
Jankowski et al[84]	Patients with CAD	562	28.1%	As per patient, interviews and examinations conducted 6–18 mo after hospitalization
Guntekin et al[85]	Patients with ACS	1026	17.5%	Up to 6 mo after hospitalization
Dyrbus et al[86]	Patients with ACS	19,287	20.7%	At hospital admission

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHD, coronary heart disease; LDL-C, low density lipoprotein cholesterol; PCI, percutaneous coronary intervention.

Previous studies suggest that control of hypercholesterolemia after hospitalization due to CHD is dependent on patient-related and clinical factors. Research has found that around 25–50% of patients discontinue statin use within 1 year of treatment initiation, which then further decreases over time. A cross-sectional study of 67,100 patients with CHD found that almost 80% of patients were adherent to statin therapy, and that LDL-C goal attainment was positively associated with adherence (85.8% achieved LDL-C <100 mg/dL and 79.8% <70 mg/dL).[88] In addition, Zhang et al[89] have identified gender, age, prior MI, prior PCI, and baseline LDL-C level as independent risk factors for LDL-C goal attainment in patients with ACS after PCI.

Poor adherence to statin therapy increases the risk for recurrent CV and non-CV events.[90] A retrospective cohort study in 29,797 adults (16,701 had CV disease) evaluated the association of treatment intensity with CV outcomes in patients with CVD. This study found the lowest CV risk to be in adherent patients receiving high-intensity therapy and the highest CV risk in nonadherent patients on low-intensity therapy.[91] To improve adherence, the provider should specifically relate the reason for prescribing medication for the patient's condition and explain the benefits of such treatment.[88] As many patients discontinue treatment because of fear of adverse effects,[81] the provider should also discuss potential side effects with the patient, explaining that statins are different from one another, and that a problem with one does not usually indicate that all statins need to be avoided.[88]

CONCLUSIONS

Dyslipidemia is a major risk factor for CVD, which is the leading cause of death globally. LDL-C is the primary lipid measurement for the evaluation of CV risk and the primary target for initiating and adjusting lipid-lowering interventions. Evidence supports the use of more intensive treatment regimens and a lower level for optimal LDL-C level in patients with ACS. The range, velocity, and duration of LDL-C reduction should be optimized in the management of patients with ACS. Attainment rates of target LDL-C levels are low and associated with poor adherence to LLT, which increases the risk of recurrent CV and non-CV events. Providers should specifically relate the reason for prescribing these agents for a patient's condition and clearly explain the benefits to the patient, while also discussing any potential adverse effects of statin therapy.

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