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

INTRODUCTION
Cardiovascular disease (CVD) is the leading cause of death globally, accounting for 31.4% of deaths in 2012. 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 risk factor for atherosclerotic CVD (ASCVD) and the primary target for the management of dyslipidemia. Furthermore, evidence from genetic and clinical studies has also identified LDL-C as a causal factor in the pathophysiology of ASCVD.

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. Studies have demonstrated that intensive statin therapy can reduce the incidence of major adverse CV events (MACE) in patients with ACS. 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. Based on this recent evidence, current guidelines on the management of dyslipidemia recommend a lower LDL-C treatment goal in secondary prevention. 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. 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%). 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. The prevalence of dyslipidemia, especially hypercholesteremia, has increased substantially over the past decade in China. A recent meta-analysis of 38 observational studies found a 41.49% overall pooled prevalence of dyslipidemia in Chinese adults. A total of 308 million people (31.5%) of the
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.\(^2\) 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.\(^2\)

In major international guidelines, LDL-C is the primary target for initiating and adjusting lipid-lowering interventions.\(^1,12,23\) 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 patients with hypercholesterolemia.\(^2\) 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.\(^2\) 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.\(^2\)

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.\(^2\) Results from pivotal trials are consistent with “the lower, the better” approach to lowering LDL-C in patients with ASCVD.\(^3\) A Cholesterol Treatment Triallists’ meta-analysis showed that reducing LDL-C by 1 mmol/L results in a 10% relative reduction in all-cause mortality.\(^4\) 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\(^5,9\) 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 pre-treatment 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)             | $\geq 50\%$ reduction from baseline and $< 1.4$ mmol/L (55 mg/dL)                | High-intensity statin therapy should be initiated early (during the first 1–4 days of hospitalization for the index ACS) | If the LDL-C target is not achieved after 4–6 weeks despite maximum tolerated statin therapy, combination with ezetimibe is recommended | 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 |
|                            | $< 40$ 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 | 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 | 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 | Safety issues need to be assessed at this time, and statin treatment doses adapted accordingly |
| ACC/AHA (2018)             | 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 $\geq 70$ mg/dL (1.8 mmol/L) and adding a PCSK-9 inhibitor if LDL-C $\geq 70$ mg/dL ($\geq 1.8$ mmol/L) on maximally tolerated statin and ezetimibe therapy | Assess adherence and percentage response to LDL-C-lowering medications and lifestyle changes |

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. 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. 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, 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. 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. 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 $\geq 4.9$ mmol/L, or diabetes). In line with the observed differences in response to statins in East Asian populations, Chinese guidelines recommend initiating moderate-intensity statin therapy. Table 2 provides an overview of recommendations from current East Asian guidelines 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 Trials’ 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). In another meta-analysis comprising 49 trials...
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.\(^9\) 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.\(^5,9\) 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

### 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)  | LDL-C target <70 mg/dL, or lowering by \(\geq 50\%\) if baseline LDL-C is high and target cannot be achieved, and by \(< 50\%\) 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)   | 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)   | 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 Ezetimibe, PCSK-9 inhibitor, and EPA have been proven to be effective for the prevention of ASCVD when used in combination with statins |
| Japan guidelines (2017)     | 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.
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.\textsuperscript{43\textendash}46 The LIPID trial initially compared pravastatin and placebo in over 9000 patients with CHD over 6 years;\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{41\textendash}48

**LDL-C–Lowering Strategies in Patients With ACS**

**Statins**

Benefits of statins in secondary prevention are well established.\textsuperscript{1} Several large RCTs of statins in secondary prevention have shown that, when compared with placebo, statin therapy significantly reduced the incidence of MACE.\textsuperscript{24,26,49\textendash}52 Most evidence demonstrates that the major benefit of statin therapy is due to lowering of LDL-C.\textsuperscript{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 \( \geq 30 \) days) by 16% and subsequent events by 19%.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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, rosvuastatin 20–40 mg and atorvastatin 40–80 mg are considered as high-intensity statins.\textsuperscript{10,11} A summary of findings from pivotal trials\textsuperscript{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 rosvuastatin 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.\textsuperscript{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.\textsuperscript{58\textendash}67 A summary of trials\textsuperscript{58\textendash}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.\textsuperscript{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 NSTEMI, 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 NSTEMI has been identified as a predictor of mortality to 5 years of follow-up.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{74} Thus, findings of these two large trials do not support routine use of statin loading doses 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

PCSX9 Inhibitors

Two recent key placebo-controlled, randomized trials with PCSX9 inhibitors added to maximum statin therapy have found a 15% relative risk reduction in the composite end point (CV 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 evolocumab 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
| Study                  | Objectives                                                                 | Population                                | Patients | Intervention                                                                                     | Results                                                                 |
|-----------------------|----------------------------------------------------------------------------|-------------------------------------------|----------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Chyrchel et al (2006) | 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) | 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. placebo 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) | 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) 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 |
| Yun et al. (2009)     | 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                                  | MACE rate at 30 days: Atorvastatin group 5% vs. 80 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) |
| Sun et al (2010)      | 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) |
| Study | Objectives | Population | Patients | Intervention | Results |
|-------|------------|------------|----------|--------------|---------|
| Yun et al. (2011)\(^a\)\(^b\) | 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)\(^c\) | 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-\(\alpha\) significantly higher in the control group Post-PCI LDL-C (nmol/L) Atorvastatin 2.02 ± 0.84 vs. 2.56 ± 0.89 |
| Wang et al (2013)\(^d\) | 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)\(^e\) | 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) | 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) | 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) | 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) | 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 | 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 DYSIS79; 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.81 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 studies17,80,81,83–86 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

| Study                          | Population                                      | Patients (n) | Percentage of Patients With LDL-C <70 mg/dL (<1.8 mmol/L) | Timing of LDL-C Laboratory Findings |
|--------------------------------|-------------------------------------------------|--------------|------------------------------------------------------------|-------------------------------------|
| DYSIS II78                     | Patients with stable CHD or ACS (ACS)            | (ACS)        | 18.9%                                                      | At hospital admission               |
| DYSIS II (French cohort)79      | Patients with stable CHD or ACS (ACS) 468        | (ACS) 468    | 16.9%                                                      | At hospital admission               |
| DYSIS II (Hong Kong and Taiwan cohort)76 | Patients with stable CHD or ACS (ACS) 270       | (ACS) 270    | 17%                                                        | At hospital admission               |
| EUROASPIRE IV82                | Patients with CAD who had CABG, PCI, or ACS      | 6648         | 19.3%                                                      | As per patient, interviews conducted 6–36 mo after the diagnosis of first or recurrent CAD |
| EUROASPIRE V83                 | 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 al84              | Patients with CAD                                | 562          | 28.1%                                                      | As per patient, interviews and examinations conducted 6–18 mo after hospitalization |
| Guntekin et al85               | Patients with ACS                                | 1026         | 17.5%                                                      | Up to 6 mo after hospitalization    |
| Dyrbus et al86                 | 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). In addition, Zhang et al. 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. 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. 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.

As many patients discontinue treatment because of fear of adverse effects, 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.

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 attainment. Evidence supports the use of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670–1681.

1. Wadhera RK, Steen DL, Khan I, et al. A review of low-density lipoprotein cholesterol, treatment strategies, and its impact on cardiovascular disease morbidity and mortality. J Clin Lipidol. 2016;10:472–489.
2. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the American Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38:2459–2472.
3. Yan BP, Chiang FT, Ambegaonkar B, et al. Low-density lipoprotein cholesterol target achievement in patients surviving an acute coronary syndrome in Hong Kong and Taiwan - findings from the Dyslipidemia International Study II. Int J Cardiol. 2018;265:1–5.
4. Cannon CP, Steinberg BA, Murphy SA, et al. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol. 2006;48:438–445.
5. Jousan K, Majumdar SR, McAlister FA. The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials. CMAJ. 2008;178:576–584.
6. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670–1681.
7. Karlson BW, Palmer MK, Nicholls SJ, et al. Doses of rosuvastatin, atorvastatin and simvastatin that induce equal reductions in LDL-C and non-HDL-C: results from the VOYAGER meta-analysis. Eur J Prev Cardiol. 2016;23:744–747.
8. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376:1713–1722.
9. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018;379:2097–2107.
10. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41:111–188.
11. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/ABC/ACP/ADA/AGS/APhA/ASP/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73:e285–e350.
12. Jacobson TA, Ito MK, Kaki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1—full report. J Clin Lipidol. 2015;9:129–169.
13. Society IA. An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia—full report. J Clin Lipidol. 2014;8:29–40.
14. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41:255–323.
15. Smith DG. Epidemiology of dyslipidemia and economic burden on the healthcare system. Am J Manag Care 2007;13:S68–S71.
16. Lin CFCY, Chien SC, Lin YH, et al. Epidemiology of dyslipidemia in South Asia Pacific region. J Jpn J Cardiol 2018;12:2–6.
17. Kuang Y, Li X, Chen X, et al. Higher prevalence of elevated LDL-C than non-HDL-C and low statin treatment rate in elderly community-dwelling Chinese with high cardiovascular risk. Sci Rep. 2016;6:34268.
18. Yang W, Xiao J, Yang Z, et al. Serum lipids and lipoproteins in Chinese men and women. Circulation. 2012;125:2212–2221.
19. Sun GZ, Li Z, Guo L, et al. High prevalence of dyslipidemia and associated risk factors among rural Chinese adults. Lipids Health Dis. 2014;13:189.
20. Huang Y, Gao L, Xie X, et al. Epidemiology of dyslipidemia in Chinese adults: meta-analysis of prevalence, awareness, treatment, and control. Popul Health Metr. 2014;12:28.
21. Abdullah SM, Defina LF, Leonard D, et al. Long-term association of low-density lipoprotein cholesterol with cardiovascular mortality in individuals at low 10-year risk of atherosclerotic cardiovascular disease. Circulation. 2018;138:2315–2325.
22. Sharrett AR, Ballantyne CM, Coudy SA, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2001;104:1108–1113.
23. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J. 2016;37:2999–3058.
24. Group SSS. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383–1389.
25. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998;339:1349–1357.

26. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352:1425–1435.

27. LaRosa JC, Grundy SM, Kastelein JJ, et al. Safety and efficacy of atorvastatin-induced very low-density lipoprotein cholesterol levels in patients with coronary heart disease (a post hoc analysis of the treating to new targets [TNT] study). Am J Cardiol. 2007;100:747–752.

28. Joint committee for guideline revision. 2016 Chinese guidelines for the management of dyslipidemia in adults. J Geriatri Cardiol. 2018;15:1–29.

29. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:e344–426.

30. Alshamiri M, Ghanaim MMA, Barter P, et al. Expert opinion on the applicability of dyslipidemia guidelines in Asia and the Middle East. Int J Gen Med. 2018;11:313–322.

31. Hu M, Thomas GN, Tomlinson B. Lipid disorders in Chinese populations. Clin Lipidol. 2011;6:549–562.

32. Pu J, Romanelli R, Zhao B, et al. Dyslipidemia in special ethnic populations. Cardiol Clin. 2015;33:325–333.

33. Naci H, Brugts JJ, Fleurence R, et al. Comparative benefits of statins for the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials. Eur J Prev Cardiol. 2013;20:641–657.

34. Zhao SP, Yu BL, Peng DQ, et al. The effect of moderate-dose versus double-dose statins on patients with acute coronary syndrome in China: results of the CHILLAS trial. Atherosclerosis. 2014;233:707–712.

35. Kinoshita M, Yokote K, Arai H, et al. Japan Atherosclerosis Society (JAS) guidelines for prevention of atherothrombotic cardiovascular diseases 2017. J Atheroscler Thromb. 2018;25:846–984.

36. Rhee EJ, Kim HC, Kim JH, et al. 2018 Guidelines for the management of dyslipidemia in Korea. Korean J Intern Med. 2019;34:723–771.

37. Li YH, Ueng KC, Jeng JS, et al. 2017 Taiwan lipid guidelines for high risk patients. J Formos Med Assoc. 2017;116:217–248.

38. China Cholesterol Education Program (CCEP) Working Committee. Atherosclerosis thrombosis prevention and Control Subcommittee of Chinese International Exchange and Promotion Association for Medical and Healthcare; Cardiovascular Disease Subcommittee of China Association of Gerontology and Geriatrics; Atherosclerosis Professional Committee of Chinese College of Cardiovascular Physicicans. China cholesterol education program (CCEP) expert advice for the management of dyslipidaemias to reduce cardiovascular risk. J Zhe Jie He Za Zhi. 2020;18:12–22.

39. Silverman MG, Ference BA, In K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA. 2016;316:1289–1297.

40. Wang Y, Yan BP, Nichol MB, et al. Real-world study of low-density lipoprotein cholesterol levels and cardiovascular outcomes in Chinese: a retrospective cohort study in post-percutaneous coronary intervention acute coronary syndrome patients. Int J Cardiol. 2017;249:18–24.

41. Miura T, Izawa A, Motoki H, et al. Clinical impact of rapid reduction of low-density lipoprotein cholesterol level on long-term outcome of acute myocardial infarction in the statin era: subanalysis of the ALPS-AMI study. PLoS One. 2015;10:e0127835.

42. Gencer B, Mach F. Lipid management in ACS: should we go lower faster? Atherosclerosis. 2018;275:368–375.

43. Strandberg TE, Pyorala K, Cook TJ, et al. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian simvastatin survival study (4S). Lancet. 2004;364:771–777.

44. LIPID Study Group (Long-term Intervention with Pravastatin in Ischaemic Disease). Long-term effectiveness and safety of pravastatin in 5,209 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. Lancet. 2002;359:1379–1387.

45. Heart Protection Study Collaborative Group. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. Lancet. 2011;378:2013–2020.
66. Jang Y, Zhu J, Ge J, et al. Preloading with atorvastatin before percutaneous coronary intervention in statin-naïve Asian patients with non-ST elevation acute coronary syndromes: a randomized study. J Cardiol. 2014;63:335–343.

67. Jiao Y, Hu F, Zhang Z, et al. Efficacy and safety of loading-dose rosuvastatin therapy in elderly patients with acute coronary syndromes undergoing elective percutaneous coronary intervention. Clin Drug Investig. 2015;35:777–784.

68. Jiang J, Zhou YJ, Li JJ, et al. Uncontrolled hyperlipidemia in Chinese patients with acute coronary syndrome after percutaneous coronary intervention. Eur J Prev Cardiol. 2016;23:636–648.

69. Jiang J, Zhou YJ, Li JJ, et al. Factors related to the effectiveness of hypercholesterolemia treatment following hospitalization for coronary artery disease. Pol Arch Med Wewn. 2016;126:388–394.

70. Jiang J, Zhou YJ, Li JJ, et al. Controlling hyperlipidemia in Chinese patients who experienced acute coronary syndrome: an observational study. Ther Clin Risk Manag. 2018;14:2255–2264.

71. Jiang J, Zhou YJ, Li JJ, et al. Uncontrolled hyperlipidemia in Chinese patients who experienced acute coronary syndrome: an observational study. Ther Clin Risk Manag. 2018;14:2255–2264.

72. Jiang J, Zhou YJ, Li JJ, et al. Controlling hyperlipidemia in Chinese patients who experienced acute coronary syndrome: an observational study. Ther Clin Risk Manag. 2018;14:2255–2264.