Current status of lipid management in acute coronary syndrome

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ABSTRACT

The development of coronary revascularization has dramatically improved early cardiovascular outcomes in patients with acute coronary syndrome (ACS). However, patients who have experienced myocardial infarction (MI) are at high risk of recurrence of cardiovascular events compared with those who are healthy or have stable coronary artery disease. Acute coronary events induce further inflammatory responses and plaque vulnerability in either a coronary culprit or whole vessels. The majority of data have supported the importance of coronary risk management to prevent secondary events. Dyslipidemia is common and one of the therapeutic targets in patients with ACS. Statins can reduce coronary plaque burden and lower the risk of cardiovascular death, recurrent MI, stroke, and coronary revascularization in patients with ACS. Growing evidence from clinical trials and meta-analyses supports early, intensive, and continuous therapy with statins in patients with ACS. Statins are accepted worldwide as the first-line lipid-lowering therapy as guidelines recommend. However, some patients do not reach the target level of low-density lipoprotein cholesterol by statins alone or are contra-indicated for statins. Recently, several clinical trials showed the further benefit of ezetimibe combined with statins on cardiovascular outcomes and coronary plaque regression in patients with ACS. In addition, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, novel and powerful lipid-lowering agents, have been developed and used in clinical settings. In this review, we summarize the present statin therapy, and refer to ezetimibe and PCSK9 as novel or additional non-statin strategies in the management of ACS.

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Introduction

Patients experiencing acute myocardial infarction (MI) are at high risk of recurrence of cardiovascular events compared with those who are healthy or have stable coronary artery disease.

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Although coronary revascularization has improved early survival rates after acute coronary syndrome (ACS), we should manage coronary risks to prevent chronic events from the early phase of ACS. The pathogenesis of ACS is a coronary plaque rupture and erosion on the intima followed by thrombus formation and further platelet reaction in the coronary artery. The inflammation induced by these processes leads to further consequences of plaque disruption. Therefore, the management of coronary risk factors and plaque stabilization is important to improve cardiovascular outcomes in ACS.

Dyslipidemia is commonly observed in patients with ACS. Particularly, low-density lipoprotein-cholesterol (LDL-C) is an established risk associated with the development of atherosclerosis and subsequent cardiovascular disease. Evidence shows that the reduction of LDL-C level prevents cardiovascular outcomes. The current pharmacological lipid managements for cardiovascular disease are mainly established by statin trials. In addition to the effect of LDL-C level reduction, statins have pleiotropic effects for coronary plaque stabilization, anti-inflammation, anti-oxidant, anti-platelet, improvement of endothelial function, and increase in adiponectin. The benefit of early and intensive lipid-lowering therapy with statins was demonstrated to improve cardiovascular events in patients with ACS. As many trials and meta-analyses have demonstrated, treatment with statins is widely accepted as the first-line lipid-lowering therapy.

Recently, novel agents for dyslipidemia began to be clinically used, and the newest European guidelines or 2016 American College of Cardiology (ACC) Expert Consensus for the management of dyslipidemia show the consideration to use of ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. This review is a digest of the current pharmacological lipid-lowering therapy in patients with ACS. We also refer to novel lipid-lowering therapies in the management of ACS.

Significance of intensive treatment and target level

Intensive lipid-lowering therapy was evaluated in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial. This study randomized patients with ACS to intensive (80 mg/day atorvastatin) or standard (40 mg/day pravastatin) lipid-lowering therapy within 10 days from the onset of ACS, and compared the cardiovascular outcomes at 24 months. The primary endpoint was a composite of all-cause death, non-fatal MI, unstable angina, revascularization, and stroke. In this study, atorvastatin significantly reduced the level of LDL-C compared with pravastatin (51% vs 22%, p = 0.0001). The atorvastatin group experienced the lower rate of the primary endpoint compared with pravastatin group (3.0% vs 4.2%, p = 0.046). PROVE IT-TIMI 22 demonstrated that intensive lipid-lowering therapy with 80 mg/day atorvastatin significantly decreased the cardiovascular outcomes compared with standard lipid-lowering therapy.

A meta-analysis, the Cholesterol Treatment Trials (CTT) which included more than 90,000 participants in 14 randomized trials of statins, also showed that a reduction of 1.0 mmol/L (38.7 mg/dL) in LDL-C level corresponds to a 23% reduction in mortality of cardiovascular disease and nonfatal MI over 5 years. This proposes the concept of the lower, the better. Furthermore, statins can relatively reduce cardiovascular events regardless of the pretreatment LDL-C level (Fig. 1).

The 2013 ACC/American Heart Association (AHA) guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults suggested a new paradigm in the management of lipids in patients with MI as it is called “fire-and-forget” strategy. This guideline recommended high-intensity statin therapy regardless of the level of LDL-C in all patients younger than 75 years with prior MI (Table 1). This high-intensity statin therapy did not set the goal level of LDL-C or the change of statin dose according to the level of LDL-C. The Japanese guideline for the management of ST elevation MI also recommends to initiate statins regardless of the level of LDL-C at the early phase of MI (Table 1). High-intensity statin use is widely acceptable from early phase of MI.

Conversely, the most recently published guideline, the 2016 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guideline for the management of dyslipidemia recommended a “treat-to-target” strategy which determines the goal of LDL-C [<1.8 mmol/L (70 mg/dL)] or at least 50% reduction from the baseline if the baseline level of LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL)] in high-risk patients including ACS (Table 1). Furthermore, the re-evaluation of the efficacy or safety of lipid-lowering therapy was recommended at 4–6 weeks after ACS. Thus, ESC/EAS guidelines recommended “treat-to-target” and newly alternative strategies in the management of patients with ACS. These guidelines and other evidence show the validity for the administration of strong statins in patients with ACS (Table 1).

Early treatment

The benefit of early statin therapy has been demonstrated in patients with ACS. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study is a randomized, double-blind, and placebo-controlled trial using atorvastatin that demonstrated the short-term efficacy of atorvastatin to reduce cardiovascular outcomes in patients with ACS. In this study, 80 mg/day atorvastatin or placebo administered within 4 weeks from hospitalization due to ACS was demonstrated to reduce by 16% death and ischemic events up to 16 weeks compared with the placebo control group. Furthermore, phase Z of the A to Z trial, a randomized, double-blind trial in 4497 patients with ACS, compared early intensive treatment and delayed and less intensive treatment using simvastatin in patients with ACS. The mean initiation time of statin was 4 days after onset of ACS. Although, this study could not demonstrate the effects by the early initiation of statins overall, early intensive treatment significantly reduced mortality, non-fatal MI, and stroke.
by 25% major cardiovascular events from 4 months through the end of this study.

In Japanese studies, the Multicenter Study for Aggressive Lipid-lowering Strategy by HMG-CoA Reductase Inhibitors in Patients with Acute Myocardial Infarction (MUSASHI-AMI) evaluated whether early statin use could decrease cardiovascular events in patients with AMI. In this study, 486 patients with AMI were randomized to receive either lipid-lowering therapy with any available statins or no statin within 96 h from the onset of AMI [6]. The primary endpoint was a composite of cardiovascular death, nonfatal MI, recurrence of symptomatic myocardial ischemia, heart failure, and stroke. Patients treated with statins were associated with significantly lower recurrence of cardiovascular events as compared with standard therapy without statins during the 2 years of follow up (6.1% vs 11.4%, \( p = 0.0433 \)).

The ACC/AHA guideline recommends the initiation of statin therapy before hospital discharge [10]. The ESC/EAS guideline clearly shows the starting timing of statin as 1–4 days of hospitalization due to ACS [7]. Japanese guidelines also recommend early statin therapy regardless of the level of LDL-C in all patients with ST elevation MI. Thus, early and intensive lipid-lowering therapy with statins is currently recommended worldwide.

### Coronary plaque change by lipid-lowering therapy

The effects of lipid-lowering therapy with statins on coronary plaque volume were evaluated in Japanese patients with ACS. In Japan, the Early Statin Treatment in Patients with Acute Coronary Syndrome (ESTABLISH) single center study demonstrated that 6 months’ treatment with 20 mg/day atorvastatin reduced mean level of LDL-C to less than 70 mg/dL, leading to 13.1% reduction of plaque volume assessed by intravascular ultrasound (IVUS) [11]. The extended-ESTABLISH study, follow-up study of ESTABLISH study, further demonstrated that the coronary plaque regression was associated with better cardiovascular outcomes in patients with ACS [12].

The Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome (JAPAN-ACS) multicenter study further evaluated the effects of statins (4 mg/day pitavastatin or 20 mg/day atorvastatin) on coronary plaque regression. Both pitavastatin and atorvastatin significantly reduced LDL-C level to 80 mg/dL, resulting in 17.5% reduction of coronary plaque volume [13]. These studies indicated that intensive lipid-lowering therapy with statins has a benefit on coronary plaque progression, leading to prevention of cardiovascular events in patients with ACS.

Other than statins: Ezetimibe

Ezetimibe targets Niemann-Pick C1-like 1 protein, and inhibits cholesterol absorption in the small intestine. The randomized Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPRESS-IT) is a landmark study to first demonstrate the impact of a non-statin lipid-lowering agent combined with the standard statin therapy on the long-term cardiovascular outcomes in patients with ACS [14]. In this study, 18,144 patients with ACS within the preceding 10 days were randomized either to ezetimibe 10 mg plus simvastatin 40 mg or to simvastatin 40 mg alone. Additional ezetimibe to simvastatin further reduced mean LDL-C level by 24% compared with simvastatin alone (53.7 mg/dL vs. 69.5 mg/dL, \( p < 0.001 \)). The primary outcome (composite of cardiovascular death, nonfatal MI, hospitalization for unstable angina, coronary revascularization, or stroke) was significantly lower in the combined treatment arm (32.7% vs. 34.7%, \( p = 0.016 \)) at 7 years. The rate of MI was significantly lower in the combined therapy arm (13.1% vs. 14.8%, \( p = 0.002 \)). Importantly, the safety and tolerability were confirmed in the combined therapy group. The reduction rate of cardiovascular events in IMPRESS-IT against the change in LDL-lowering was plotted on the regression line from previous statin trials, reconfirming the concept of "LDL hypothesis" (Fig. 1) [4]. The pivotal study demonstrated that intensive LDL-C lowering therapy with ezetimibe has a benefit on ACS.

We recently reported the result of a prospective, randomized, controlled, and multicenter trial, the Plateau REGression with Cholesterol absorption Inhibitor or Synthesis inhibitor Evaluated by Intravascular UltraSound (PRECISE-IVUS). This study evaluated the effect of additional ezetimibe to statin on coronary plaque in Japanese patients with ACS or stable coronary disease who underwent percutaneous coronary intervention [15]. In PRECISE-IVUS study, ezetimibe added to atorvastatin significantly associated with further LDL-C level reduction and coronary plaque regression (LDL-C, 63.2 mg/dL vs. 73.3 mg/dL, \( p < 0.001 \); coronary plaque regression rate, \(-1.4% \) vs. \(-0.3\%\), \( p = 0.001 \)). In patients with ACS, coronary plaque regression was further reduced in ezetimibe added to atorvastatin therapy (\(-2.3\% \) vs. \(-0.2\%\), \( p < 0.001 \)).

The 2016 ACC Expert Consensus or European guidelines show the consideration of ezetimibe combined with statins if the LDL-C has not reached the target level with high tolerable dose of statins [7,8].

Although the US Food and Drug Administration considers that statins remain the first-line lipid-lowering therapy because of insufficient evidence of the comparison between ezetimibe and statins, growing evidence supports the efficacy of ezetimibe combined with statins in patients with ACS.

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**Table 1** Comparison of guidelines regarding acute coronary syndrome.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Strategy or the target level of LDL-C</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan, 2012</td>
<td>&lt;2.6 mmol/L (100 mg/dL)</td>
<td>High-intensity statins: Atorvastatin, 40–80 mg, or Rosuvastatin, 20–40 mg</td>
</tr>
<tr>
<td>ACC/AHA, 2013 [10] Expert</td>
<td>≤75 years old High-intensity statin therapy which lowers LDL-C, on average by approximately &gt;50%</td>
<td>Moderate-intensity statin therapy which lowers LDL-C, on average by approximately 30–50%</td>
</tr>
<tr>
<td>Consensus, 2016 [8]</td>
<td>High-intensity statin therapy which lowers LDL-C, on average by approximately &gt;50%</td>
<td></td>
</tr>
<tr>
<td>ESC/EAS, 2016 [7]</td>
<td>High-intensity statin therapy: &lt;1.8 mmol/L (70 mg/dL), or ≤50% LDL-C (70 and 135 mg/dL)</td>
<td>Moderate-intensity statin therapy: Atorvastatin, 10–20 mg, Rosuvastatin, 5–10 mg, Simvastatin, 20–40 mg, Pravastatin, 40–80 mg, Lovastatin, 40 mg, Fluvastatin XL, 80 mg, Fluvastatin, 40 mg twice daily, or Pitavastatin, 2 to 4 mg</td>
</tr>
</tbody>
</table>

LDL-C: low-density lipoprotein cholesterol; ACC/AHA, American College of Cardiology/American Heart Association; ESC/EAS, European Society of Cardiology; European Atherosclerosis Society.
<table>
<thead>
<tr>
<th>Agents</th>
<th>Trial</th>
<th>Phase</th>
<th>Participants</th>
<th>Population</th>
<th>Dosage</th>
<th>Start date</th>
<th>Completion date</th>
<th>Primary outcome</th>
<th>Observation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab</td>
<td>ODYSSEY Outcomes</td>
<td>Phase III</td>
<td>18,000</td>
<td>Experienced ACS 4 to 52 weeks prior to randomization</td>
<td>Subcutaneous every 2 weeks</td>
<td>October 2012</td>
<td>February 2018</td>
<td>Cardiovascular death, non-fatal MI, UA requiring hospitalization, fatal and non-fatal ischemic stroke</td>
<td>64 months</td>
</tr>
<tr>
<td>PCSK9 inhibitors</td>
<td>Alirocumab ODYSSEY J-IVUS</td>
<td>Phase IV</td>
<td>200</td>
<td>Hospitalized for ACS - LDL-C ≥100 mg/dL - Patients who undergo intravascular ultrasound imaging with coronary stenosis (≥50%) angiographically within 1 week after the onset of ACS - Aged ≥20 years old at ACS diagnosis</td>
<td>Subcutaneously every 2 weeks</td>
<td>November 2016</td>
<td>September 2018</td>
<td>Percent change (normalized total atheroma volume)</td>
<td>36 months</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>FOURIER</td>
<td>Phase III</td>
<td>27,000</td>
<td>History of clinically evident of CVD - LDL-C ≥70 mg/dL (1.8 mmol/L) or non-HDL-C ≥100 mg/dL (2.6 mmol/L) - Triglycerides ≤400 mg/dL (4.5 mmol/L)</td>
<td>Subcutaneous every 2 weeks or every 4 weeks</td>
<td>February 2013</td>
<td>November 2016</td>
<td>Cardiovascular death, MI, Stroke, UA requiring hospitalization, coronary revascularization</td>
<td>5 years</td>
</tr>
<tr>
<td>CETP inhibitor</td>
<td>Anacetrapib REVEAL</td>
<td>Phase III</td>
<td>30,000</td>
<td>&gt;50 years old - History of MI, cerebrovascular disease, - Peripheral arterial disease, or diabetic patients with other evidence of symptomatic coronary heart disease</td>
<td>Tablet 100 mg daily</td>
<td>June 2011</td>
<td>January 2017</td>
<td>Coronary death, MI or coronary revascularation</td>
<td>4 years median</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; MI, myocardial infarction; UA, unstable angina; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; CETP, cholesteryl ester transfer protein.
Other than statins: PCSK9 inhibitors

PCSK9 regulates the lipid metabolism via promoting the catabolism of LDL receptors. Blocking of PCSK9 inhibits degradation of LDL receptors, leads to LDL-C clearance from blood. PCSK9 inhibitors are novel powerful lipid-lowering agents for familial hyperlipidemia, statin intolerance, and patients who do not reach the goal of lipid-lowering therapy at high risk for cardiovascular events. Clinical studies have shown that PCSK9 inhibitors reduce LDL-C by as much as 40–70% when added to maximally tolerated statin [16]. It is suggested that PCSK9 levels are upregulated by myocardial ischemia, and are associated with coronary plaque vulnerability. The inhibition of PCSK9 is expected as a novel strategy in ACS due to its pleiotropic effects [17].

Promising data for efficacy of PCSK9 inhibitors on clinical outcomes were reported from a meta-analysis of 24 phase II or III randomized, controlled trials, including 10,159 patients with familial, nonfamilial, or unspecified hypercholesterolemia [16]. Patients in this meta-analysis, users of PCSK9 antibodies compared with no anti-PCSK9 users were associated with lower odds of all-cause mortality (OR, 0.50; 95% CI, 0.23–1.10; p = 0.084) and MI (OR, 0.49; 95% CI, 0.26–0.93; p = 0.030).

Recently, the result of Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLACOV) trial was published. This multicenter, double-blind, placebo-controlled, randomized trial evaluated the effects of PCSK9 inhibitor with evolocumab, fully human monoclonal antibody, on coronary plaque in patients treated by statins during 78 weeks [18]. Patients with previous MI were included in this study (35%). Evaluable followed-up images among 846 patients demonstrated that evolocumab significantly reduced LDL-C level (36.6 vs. 93.0 mg/dl; p < 0.001) and coronary plaque volume (64.3% vs. 47.3%; p < 0.001) compared with placebo. Serious adverse events were not significantly different between the placebo and the evolocumab-treated group. The 2016 ACC Expert Consensus and European guidelines show the consideration of PCSK9 inhibitors if the LDL-C does not reach the target level with high tolerable dose of statins and/or ezetimibe [7,8]. The Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES, NCT01663402), and Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER, NCT01764633) studies using evolocumab are ongoing in patients with post-ACS and high risk of cardiovascular events worldwide (Table 2). Also in Japan, ODYSSEY-J-IVUS trials started in ACS patients with insufficient LDL-C control by statins to evaluate the progression or the regression of coronary plaque using alirocumab (NCT02984982, Table 2). Bococizumab, humanized monoclonal antibody to PCSK9 was also expected for clinical development, but the development discontinuation was announced due to its side effects and less long-term efficacy in November 2016.

Lipid targets other than LDL-C and management

Other lipid profiles including high-density lipoprotein cholesterol (HDL-C) and triglycerides are associated with cardiovascular events [19]. In a post hoc analysis of PROVE-IT-TIMI 22, low level of HDL-C and high level of triglycerides were associated with cardiovascular events [20]. However, two large trials, which did not target ACS, failed to demonstrate the benefit of fenofibrate monotherapy or that combined with statins on preventing cardiovascular events in diabetic patients [21,22]. In addition, fibrates combined with statins are not recommended because of the risks of rhabdomyolysis and hepatotoxicity.

Niacin can also improve HDL-C and triglycerides. However, two large trials concluded that the benefit of niacin combined with statins was not observed [23,24]. On the contrary, since niacin increased serious adverse events [24], niacin is not currently approved.

It has been reported that eicosapentaenoic acid (EPA) not only improves lipid profile but also has anti-inflammatory and anti-atherogenic effects [25]. The Japan EPA Lipid Intervention Study (JELIS), which excluded patients with ACS, demonstrated that EPA addition to statin prevented cardiovascular events [26]. However, a study reported EPA did not reduce cardiovascular events in patients with MI [27]. It is unclear how we treat low HDL-C and high triglycerides in ACS. It requires further evaluation.

Next-generation agents for dyslipidemia

Cholesterol ester transfer protein (CETP) is expected to be a novel target for lipid control. CETP transfers cholesteryl esters and triglycerides from HDL-C to apolipoprotein B – containing lipoproteins including very-low-density lipoprotein. CETP increases in the acute phase of MI and leads to adverse outcomes [28]. Although CETP inhibitors were expected, several studies regarding CETP inhibitors have failed to demonstrate their benefit [29,30]. The Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification (REVEAL, NCT01252953) phase III trial using TA-8995 is ongoing (Table 2).

Furthermore, several agents, ALN-PCS, small interfering RNA of PCSK9, selective peroxisome proliferator-activated receptor (PPAR) modulator which reduces triglyceride and increases HDL-C, microsomal triglyceride transfer protein inhibitor which reduces LDL-C and apolipoprotein B, or volanesorsen (formerly INONIS-APOCIIIRx) which reduces apolipoprotein C-III, are being developed as the next-generation lipid managements. These agents are expected to decrease residual risks that statins could have not suppressed.

Conclusions

Treatment with statins is widely accepted as the first-line lipid-lowering therapy as many trials and meta-analyses have demonstrated. Although there are different concepts between “fire-and-forget” and “target-to-treat”, early and intensive administration of statins consistently contribute to the reduction of
cardiovascular events after ACS. Previous studies have not demonstrated the benefit of lipid-lowering agents except statins on improvement of cardiovascular outcomes. However, growing evidence supports that ezetimibe or PCSK9 is acceptable in those who are not able to reach the goal level of LDL-C or who are intolerant to statins after ACS [7]. Several studies targeting PCSK9, CETP, PPAR, apolipoprotein B, or apolipoprotein C-III are also ongoing, and several trials show hopeful results. It is now expected that the management of lipid-lowering therapy would move to next era (Fig. 2).

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References