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Review

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.

Contents

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 [1]. 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 [2,3]. The benefit of early and intensive lipid-lowering therapy with statins was demonstrated to improve cardiovascular events in patients with ACS [2–6]. 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 [7,8]. 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%, $p < 0.0001$) [3]. The atorvastatin group experienced the lower rate of the primary endpoint compared with pravastatin group (3.0% vs 4.2%, $p = 0.046$) [3]. 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 [4]. 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) [4,9].

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) [10]. 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.

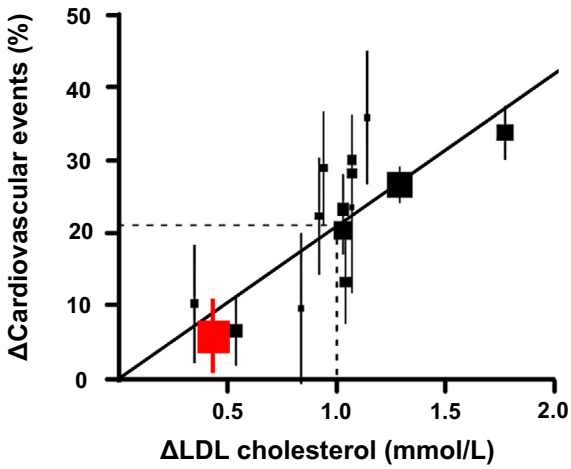

Fig. 1. Relation between proportional rate reduction of cardiovascular events and mean low-density lipoprotein (LDL) cholesterol reduction at 1 year [4,14]. Each square represents a single trial plotted for the rate of cardiovascular events and mean LDL cholesterol reduction at 1 year. Vertical lines represent SE. The regression line represents the reduction rate related with cardiovascular events and LDL cholesterol. The red square and vertical line represent the result of IMPROVE-IT [14].

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) [7]. 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 [2]. In this study, 80 mg/day atorvastatin or placebo administered within 4 days 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 [5]. 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