New LDL-Cholesterol Lowering Therapies: Pharmacology, Clinical Trials, and Relevance to Acute Coronary Syndromes

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Abstract
Background
Reduction in plasma low-density lipoprotein cholesterol (LDL-C) is a fundamental treatment for the prevention of acute coronary syndromes (ACS). Although statin therapy confers significant protection against ACS in both primary and secondary prevention, a considerable residual risk remains after intensive therapy. In addition, a significant proportion of high-risk patients do not achieve the optimal LDL-C goal recommended in the current guidelines (<1.8 mmol/L). Hence, novel LDL-C-lowering agents that act via mechanisms distinct from HMG-CoA reductase inhibition are under investigation.

Objective
We reviewed the recent literature on the development of novel LDL-C-lowering agents that could potentially be used as an alternative or adjunct to statin therapy in high-risk coronary patients.

Methods
PubMed and Scopus databases were searched to retrieve studies on the efficacy and/or tolerability of novel LDL-C-lowering agents in animals and humans.

Results
Agents that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9), apolipoprotein (apo) B, and microsomal triglyceride transfer protein (MTTP) are the most promising therapies. Inhibition of PCSK9, apoB, and MTTP has been achieved mostly via fully humanized monoclonal antibodies (mAbs), antisense oligonucleotides, and synthetic compounds, respectively. PCSK9 inhibitors increase the hepatic uptake of LDL-C, while apoB and MTTP inhibitors decrease the synthesis and secretion of apoB-containing lipoproteins. These 3 mechanisms lead to marked reductions in plasma LDL-C in patients with hypercholesterolemia at risk for ACS, particularly those with familial hypercholesterolemia. Moreover, these agents can exert additional benefits by decreasing plasma levels of apoB, triglycerides, and lipoprotein(a). Mipomersen and lomitapide have been approved by the United States Food and Drug Administration (US FDA) for use in patients with homozygous familial hypercholesterolemia. PCSK9 inhibitors are currently under final evaluation in clinical outcomes studies and are anticipated to find wide application either as monotherapy or as an adjunct to statins. A main safety concern is the risk for hepatic steatosis with apoB and MTTP inhibitors, which needs to be explored in prospective, long-term trials.

Conclusions
PCSK9, apoB, and MTTP inhibitors can exert potent reductions in plasma LDL-C and apoB concentrations, either as monotherapy or in combination with statins. These effects are particularly relevant to high-risk individuals with marked hypercholesterolemia, such as those with familial hypercholesterolemia. Although the use of mipomersen and lomitapide is limited to severe familial hypercholesterolemia as a replacement for LDL-apheresis, PCSK9 inhibitors are likely to be more widely prescribed in patients at high risk for CVD, especially those who are resistant to or intolerant of high-intensity statin therapy. PCSK9 mAbs are efficacious and have an excellent safety profile, but their long-term impact on cardiovascular events is currently under investigation. Whether PCSK9 mAbs decrease the rates of recurrent cardiovascular events within 3 months following ACS is questionable; however, these agents, unlike statins, may not have pleiotropic benefits on the unstable plaque.

Key words: antisense oligonucleotide, dyslipidemia, hypercholesterolemia, monoclonal antibody, myocardial infarction, unstable angina

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