



## Review article

## Current and future trends in the lipid lowering therapy



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## ABSTRACT

Atherosclerosis is an inflammatory disease that affects arterial wall. It leads to wall thickening and its instability. As a result a reduction in lumen diameter and blood flow is observed. This manifests predominantly as the affection of vascular bed of coronary (myocardial infarction), cerebral, carotid (ischemic stroke) or peripheral arteries (limb amputation).

One of the most important factors that accelerate atherosclerosis is hyperlipidemia. According to current guidelines the main attention should be focused on the treatment of hyperlipidemia (beside the prevention, which includes proper diet, physical activity and risk factors avoidance). Major attention is given to LDL (low-density lipoprotein) cholesterol (LDL-C) level as primary, and triglyceride level as secondary targets of therapy.

As a result of recent clinical findings and continuous research in the field of hypolipidemic drugs it seems practical to review recent data and show potential new pathways that may be useful in the treatment of hyperlipidemia.

The review is divided into several parts presenting the widely used and well-known hypolipidemic drugs. In the first part a brief review of contemporary drugs affecting LDL cholesterol is shown. The second part contains information regarding currently available drugs reducing triglycerides level. The third part describes several novel and promising groups of drugs that are still on various steps of clinical development. In the last part drugs affecting HDL (high-density lipoprotein) level were presented.

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## Introduction

Atherosclerosis is an inflammatory disease that affects arterial wall and leads to the narrowing of the vessels. This manifests predominantly as myocardial infarction (coronary arteries), ischemic stroke (cerebral or carotid arteries) and limb amputation (peripheral arteries). Cardiovascular diseases (CVD) are a leading cause of mortality worldwide. 2 million people die as a result of CVD in European Union [1]. These numbers give rise to intensification of health services' effort, which should be focused on the dietary habits change, increase of physical activity accompanied by pharmacological support. Currently, despite increasing efforts in the patients' treatment, we are still observing higher level of CVD in certain populations. This specific risk is called the residual risk [2] and it is thought to be still modifiable with further reduction in the level of currently known risk factors (e.g. LDL-C) [3] or by influence on novel risk factors [e.g. lipoprotein (a)] [4].

One of the most important factors that accelerate atherosclerosis is hyperlipidemia, although one must remember that the background of this condition is multifactorial and the prevention or the reduction of the disease progression may be achieved by a complex therapeutic approach including suitable diet, physical activity and avoidance of certain risk factors (e.g. cigarette smoking). Primary efforts in hypolipidemic therapy should be focused on the lowering of the LDL-C level, while triglycerides (TG) lowering treatment is secondary to LDL-C [2,3], with the exception of extremely elevated TG level >440 mg/dL that is connected with the acute pancreatitis. The reason arises from results of multiple studies clearly showing improved cardiovascular outcomes which correlate with the reduction in LDL-C [5]. TG are also associated with atherosclerosis [2,3], but findings of clinical studies that dealt with the reduction of TG are less convincing. Nevertheless without any doubt highly elevated TG are the cause of potentially fatal acute pancreatitis [6]. Furthermore high TG are commonly connected with poorly controlled type 2 diabetes mellitus and one of the markers of atherogenic dyslipidemia, which is described as low level of HDL cholesterol (HDL-C), high level of TG and moderately increased LDL-C, rich in apo B-100 (i.e. small dense LDL) and leads to accelerated atherosclerosis [7].

Currently available drugs are effective in improving of lipid profile. Unfortunately not all of the patients may benefit from them (e.g. due to side effects excluding drugs from treatment or patient's genetic background leading to severe hyperlipidemia). Therefore several new pathways are explored to further reduce the lipids level and as a result to improve patients' outcome.

There are several comprehensive guidelines for the treatment of hyperlipidemia [8,9]. They focus mainly on LDL-C level as a main risk factor for accelerated atherosclerosis. Generally speaking all experts agree on the fact that currently the best method to obtain reduction in cardiovascular events is the reduction in LDL-C, both in primary and secondary prevention. According to the European

Atherosclerosis Society and European Association of Cardiology (EAS/ESC) guidelines, the goal of therapy should be established using SCORE (Systematic COronary Risk Evaluation) charts and anamnesis [8]. Hypertriglyceridemia should be treated as a secondary objective and it becomes primary goal of therapy in case of TG level >440 mg/dL, when the risk of acute pancreatitis is significantly elevated. Contrary to European guidelines, the American Heart Association (AHA) issued recommendation for the treatment of hyperlipidemia that focuses on the maximizing statin use in population at risk [9]. These experts reasoned that prior to the publication of their guidelines no other therapy added to statin regimen improved patient outcome, therefore only high dose statin is the option for treatment of hyperlipidemia and intensification of lipid lowering therapy with other drugs is futile. Most potent statins (rosuvastatin and atorvastatin) at high doses reduce the LDL-C level by 55–60%. However in June 2015 results of IMPROVE-IT study were published and showed that further reduction of LDL-C by addition of ezetimibe to simvastatin may improve patients' outcome [10].

Recent clinical findings and continuous research in the field of hypolipidemic drugs urged authors to perform the review of recent data and show potential new pathways (Fig. 1) that may be useful in the treatment of hyperlipidemia. To simplify the assimilation of the information, review is divided into several parts. The first two present LDL-lowering and TG-lowering drugs that are currently available on the market. In the next part new groups of drugs are described, which are still in development but may become valuable therapeutic option. The last part contains information regarding drugs affecting HDL level.

## Currently available drugs in the treatment of hypercholesterolemia

### HMG-CoA reductase inhibitors (statins)

Statins are drugs of choice in the treatment of hyperlipidemia, both in hypercholesterolemia and atherogenic dyslipidemia. Clinical benefits associated to statin treatment lead to significant reductions in LDL-C level and in the cardiovascular risk in various groups of patients [11]. With the most potent statins (rosuvastatin or atorvastatin) LDL-C level may be reduced up to 55–60%, which is accompanied by a 30% decrease in TG level. However since several years, a debate had been started regarding an increase in the incidence of diabetes. According to recent meta-analysis data the risk increase is around 9% [12]. Despite this phenomenon, statins should be used in patients with diabetes for their undeniable benefits and the fact that the increase in diabetes occurrence is of lesser concern than the decrease in CVD risk. However, in people at risk of developing diabetes regular check-ups should be scheduled in order to initiate proper treatment [13].

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