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# Statins Alone or in Combination with Ezetimibe or PCSK9 Inhibitors in Atherosclerotic Cardiovascular Disease Protection

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## Abstract

Statins have proved to be very effective in reducing atherosclerotic cardiovascular disease (ASCVD) risk, with no apparent threshold at which low-density lipoprotein cholesterol (LDL-C) lowering is not associated with a reduced risk. Yet, several meta-analyses of statin trials show significant on-treatment residual risk of major cardiovascular (CV) events. This finding points to the unmet needs, in terms of LDL-C targets and ASCVD protection, of statin-treated patients, raising the question of statin combination therapy. Ezetimibe is a cholesterol absorption inhibitor, with the potency to decrease LDL-C for about 10–18%, apolipoprotein B (apoB) for 11–16%, while, in combination therapy with statins, leads to an additional LDL-C lowering of 25%, with a total LDL-C lowering of 34–61%. It is also estimated that 10–20% of patients on statin treatment cannot tolerate them. As a result, adequate doses to achieve treatment target, or as recommended for the patient-specific risk profile, cannot be prescribed. Proprotein convertase subtilisin/kexin type 9 (PCSK9) Inhibitors are monoclonal antibodies that inhibit the binding of PCSK9 to LDL-C receptors. Besides a very potent lipid-lowering effect, PCSK9 inhibitors have added ASCVD risk reduction benefit due to a very aggressive LDL-C lowering action, especially beneficial in patients who are intolerant to statins.

**Keywords:** hyperlipidemia, statins, ezetimibe, PCSK9 inhibitors, cardiovascular diseases, cerebrovascular disease, prevention, adverse effects, diabetes, residual risk

## 1. Introduction

Atherosclerotic cardiovascular disease (ASCVD), including its clinical manifestations, such as myocardial infarction (MI) and ischemic stroke (IS), is the leading morbidity and/or mortality cause worldwide. One of the most highly studied factors associated with ASCVD is low-density lipoprotein (LDL). Vast evidence has postulated that cholesterol-rich LDL and other apolipoprotein B (apoB)-containing lipoproteins (very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL), and lipoprotein(a) [Lp(a)]), are directly involved in the development of ASCVD [1].

Statins are the first-line anti-lipemic pharmacotherapy, having been shown to reduce both LDL-C levels and cardiovascular (CV) events. However, a considerable

number of statin-treated patients do not achieve target LDL-C levels, even after maximal statin dose-treatment, or are intolerant to intensive statin therapy [2].

In the aforementioned situations patients can largely benefit from an additional LDL-C lowering agent. Ezetimibe is a non-statin drug that can additionally reduce ASCVD risk, when added to a statin, leading to a total of 34–61% LDL-C reduction [3]. Proprotein Convertase Subtilisin-Like/Kexin Type 9 (PCSK9) inhibitors, one of the newest anti-lipemic agents, can lower LDL-C by 45–65%, and are also proven to have ASCVD risk reduction properties [4].

Therefore, the aim of this chapter is to address the question of therapeutic efficacy, as expressed through the lipid-lowering and anti-inflammatory effects, and atherosclerotic cardiovascular disease risk reduction when adding ezetimibe or PCSK9 inhibitors to statin therapy.

### **1.1 HMG-CoA reductase inhibitors—statins**

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, commonly known as statins, have been one of the most frequently prescribed medications worldwide, since their introduction 30 years ago. Currently, there are six statin drugs available on the market—pitavastatin, atorvastatin, rosuvastatin, pravastatin, simvastatin and fluvastatin [5].

Statins are competitive, reversible inhibitors of HMG-CoA reductase, a rate-limiting step in the process of cholesterol biosynthesis. HMG-CoA is a microsomal enzyme—reductase which catalyzes the conversion of HMG-CoA to L-mevalonate and coenzyme A. Inhibiting the HMG-CoA reductase, statins ultimately prevent the endogenous cholesterol production. Cholesterol concentration reduction triggers an up-regulation of the expression of low-density lipoprotein (LDL)-receptors in the hepatocytes, promoting uptake of LDL and LDL-precursors from the systemic circulation. Therefore, a significant part of the statins' cholesterol-lowering action is a result of an indirect increase in LDL clearance from plasma. Additional mechanisms of action include inhibition of the hepatic apolipoprotein B100 synthesis, and a reduction of the synthesis and secretion of triglyceride-rich lipoproteins [6].

Statins are composed of two parts, the pharmacophore, a dihydroxyheptanoic acid segment, and a moiety composed of a ring system with various substituents. According to the chemical modification of the ring system and the nature of its substituents, different statin structures are generated. Ring substituents define the solubility of the statins, along with many of their pharmacological properties. Among the statins, lovastatin, simvastatin, atorvastatin, and fluvastatin are lipophilic, whereas pravastatin and rosuvastatin are more hydrophilic. Different chemical structures lead to different pharmacokinetic properties, pharmacological effects and pleiotropic actions [7].

Statins can enter the systemic circulation passively, through the intestinal cells, and actively via the ATP-binding cassette (ABC) and solute carrier (SLC) transporters. Two enzyme groups are involved in statin metabolism, the cytochrome P450 (CYP450), and UDP-glucuronosyltransferase (UGT), mainly acting in the liver, and to a lesser extent, in the kidneys. Lipophilic statins are transported via passive diffusion, metabolized by the CYP450 enzymes, and mainly excreted through the biliary system. Hydrophilic statins enter the liver via active transport, and are actively excreted through the kidneys, mostly as unchanged drugs. Lipophilic statins have generally low bioavailability due to first pass metabolism. Absorption varies between 30 and 98%, and time to reach peak plasma concentration (T<sub>max</sub>) is within 4 h of administration. Statins are administered orally as active hydroxy acids, except for lovastatin and simvastatin, which are administered as lactone pro-drugs, and then hydrolyzed to the hydroxy acid form. Their bioavailability varies;

pitavastatin has a bioavailability of 80%, whereas fluvastatin between 19 and 29%. The CYP3A4 isoenzyme is responsible for the metabolism of lovastatin, simvastatin and atorvastatin. Their active metabolites—2-hydroxy- and 4-hydroxy-atorvastatin acid from atorvastatin, and  $\beta$ -hydroxy simvastatin acid from simvastatin, carry a part of their inhibitory activity. Fluvastatin is mainly metabolized by the CYP2C9 isoenzyme. Pravastatin is eliminated by both the kidney and liver, mostly as an unchanged drug [6–8].

## 1.2 Cholesterol absorption inhibitors—ezetimibe

Ezetimibe, a cholesterol absorption blocker, has been the focus of many trials supporting its use in ASCVD risk reduction. For patients that cannot achieve target treatment goals with statin therapy alone, ezetimibe has proven to be a safe, well-tolerated medication which, combined with statins, leads to additional LDL-C reduction, thus resulting in a significant morbidity and/or mortality benefit [9].

Serum cholesterol is derived from two major sources: cholesterol synthesized *de novo* in the liver and cholesterol that has been absorbed from the gastrointestinal tract. Statins reduce serum cholesterol by reducing its biosynthesis in the liver. Ezetimibe, on the other hand, targets gastrointestinal cholesterol absorption. Ezetimibe acts at the brush boarder of the small intestine, by selectively inhibiting the cholesterol transport protein Niemann Pick C1 like 1 protein (NPC1L1), thus preventing uptake of intestinal luminal cholesterol micelles into the enterocytes. The reduced cholesterol uptake leads to hepatic LDL-C stores depletion, resulting in upregulation of hepatic LDL receptors, causing LDL-C clearance from the blood. It is also suggested that ezetimibe inhibits the hepatic NPC1L1 as well, thus leading to reduced hepatic cholesterol absorption [3, 10, 11].

Following ingestion, the drug is extensively (>80%) metabolized to its active form—ezetimibe-glucuronide. Glucuronidation of the 4-hydroxyphenyl group, by uridine 5'-diphosphate-glucuronosyltransferase isoenzymes, forms the major ezetimibe metabolite in the intestine and liver. Total ezetimibe (sum of 'parent' ezetimibe plus ezetimibe-glucuronide) concentrations reach a maximum 1–2 h after administration. Both the parent compound and the glucuronidated compound are absorbed, and recirculated via the hepatobiliary excretion, thus providing long-term cholesterol absorption inhibition. This cycle accounts for the long half-life of ezetimibe—about 22 h, allowing for once-a-day dosing. About 10–15% of the drug is excreted in the urine, and the rest in the feces, mainly as the parent drug. Ezetimibe does not appear to be metabolized or interact with the cytochrome P450 pathway, thus it does not affect bioavailability and kinetics of commonly used drugs that are affected by the CYP450 family [10, 12].

## 1.3 Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

The discovery of PCSK9 in 2003 opened many new research directions in the cardiovascular field. Liver PCSK9 binds to the LDL receptor (LDL-R) and promotes its degradation in the endosomal/lysosomal pathway. Higher PCSK9 activity leads to lower liver LDL-R levels, resulting in reduced LDL-uptake from circulation, and thus in hypercholesterolemia [13].

This led to a conclusion that the inhibition of PCSK9 would mean that more LDL receptors would be recycled to the surface of the cell, thus increasing the clearance of LDL cholesterol from the circulation. Since then various approaches to the pharmacological inhibition of PCSK9 have been investigated, and parenteral anti-PCSK9 monoclonal antibodies (MoAbs) have been the most successful strategy to date. MoAbs are now in late-stage (phase 3 clinical trials) testing [14].



Anti-PCSK9 MoAbs are known to bind at or near PCSK9's binding site for the LDL-R. This sterically inhibits the interaction of PCSK9 with the LDL-R, thus reducing the degradation of the receptor. This markedly increases the clearance of LDL and substantially lowers plasma LDL cholesterol, as well as apolipoprotein-B100 [15]. In 2015, the Food and Drug Administration (FDA) approved the PCSK9 inhibitors alirocumab and evolocumab for patients with clinical atherosclerotic cardiovascular disease on maximally tolerated statin therapy who "require additional lowering of LDL-C" [16].

Evolocumab is a human monoclonal immunoglobulin G2 antibody directed against the circulating PCSK9 protein. Evolocumab is administered by subcutaneous injection to the abdomen, thigh, or upper arm. For patients with primary hyperlipidemia, who have clinical ASCVD, or heterozygous familial hypercholesterolemia, the recommended subcutaneous dose is 140 mg every 2 weeks or 420 mg once monthly. Maximum suppression of circulating unbound PCSK9 is seen after 4 h. Peak serum concentrations are obtained in 3–4 days, with an estimated bioavailability of 72%. The drug is estimated to have an effective half-life of 11–17 days [17].

Alirocumab is a human monoclonal immunoglobulin G1 [IgG1] isotype antibody that binds to circulating PCSK9, thus inhibiting its action on LDL-R. Alirocumab reduces free PCSK9 in a concentration-dependent manner. Following a single subcutaneous administration of alirocumab 75 or 150 mg, maximal suppression of free PCSK9 occurs within 4–8 h. Within 4–8 weeks after initiating or titrating alirocumab therapy, LDL-C levels should be tested to determine the response and the need for (additional) dose adjustments. The drugs' median apparent half-life at steady state is 17–20 days. Peak serum concentrations are obtained in 3–7 days, with an estimated bioavailability of 85%. At low concentrations, the elimination of alirocumab occurs predominately via saturable binding to PCSK9. At higher concentrations, elimination is through a nonsaturable proteolytic pathway [18].

## **2. Effects of statins**

### **2.1 Effects of statin therapy on LDL-C concentrations**

During the past 20 years, the extensive use of statin therapy among patients known to have an occlusive vascular disease, or are considered to be at increased risk of cardiovascular events, has been associated with descending actions on LDL and total cholesterol concentrations [19].

Different statins have different potencies, with the newer agents (e.g., atorvastatin and rosuvastatin) able to produce larger reductions in LDL cholesterol per mg of drug, compared to the older agents (e.g., simvastatin and pravastatin). Each dose doubling leads to an additional reduction of about 6 percentage points in LDL cholesterol (e.g., 43 vs. 49% reductions with atorvastatin 20 vs. 40 mg daily). The American College of Cardiology/American Heart Association (ACC/AHA) 2013 Blood Cholesterol Guideline classified statin regimens as being of low intensity (e.g., <30% LDL-C reduction with simvastatin 10 mg daily), moderate intensity (e.g., 30% to <50% reduction with simvastatin 20–40 mg, atorvastatin 10–20 mg, or rosuvastatin 5–10 mg daily), or high intensity (e.g., ≥50% reduction with atorvastatin 40–80 mg or rosuvastatin 20–40 mg daily) [20].

High-intensity statin therapy would be expected to reduce LDL-C by at least 2 mmol/L in individuals with LDL-C concentrations of 4 mmol/L or more, but by only about 1 mmol/L in those presenting with concentrations of 2 mmol/L. Consequently, since vascular events rates reductions, in patients treated with statins, are related to the absolute reductions in LDL-C, intensive statin

treatment should be used in individuals at higher risk of vascular events, rather than just on those with high cholesterol concentrations [21].

The Cholesterol Treatment Trialists' (CTT) Collaboration was settled to conduct meta-analyses of randomized controlled statin-oriented trials involving at least 2 years of treatment in at least 1000 patients. During the study treatment periods (on average 5 years), the average LDL-C reduction was about 1–1.5 mmol/L, comparing routine statin therapy vs. no routine statin therapy, with an additional LDL-C reduction of about 0.5 mmol/L in the trials comparing allocation to more vs. less intensive statin regimens. To summarize, an intensive statin regimen, compared to no statin therapy, reduced LDL-C concentrations by 1.5–2 mmol/L [22, 23].

## 2.2 Reductions in major vascular event (MVE) rates

Statins have been proven to be very effective in reducing ASCVD risk, with no apparent threshold at which LDL-C lowering is not associated with reduced risk. The Atherosclerosis Risk in Communities (ARIC) study, performed on 13,342 individuals, provided evidence that protection against ASCVD happens in a graded fashion with LDL-C level [24]. The CTT meta-analyses detected about 25,000 major vascular events (MVE) (composite of coronary deaths or non-fatal myocardial infarctions, strokes of any type, and coronary revascularisation procedures). Comparing routine vs. no routine statin treatment, there was a 20% proportional reduction in the MVE rate per mmol/L LDL-C reduction. Regarding the comparison of more vs. less intensive statin regimens, the average 0.5 mmol/L further LDL-C reduction lead to an additional 15% proportional reduction in the MVE rate [22, 23].

By combining the findings from the two previously mentioned sets of trials, it can be concluded that a LDL-C concentration reduction by 2 mmol/L would reduce the MVE risk by about 45%. Given the aforementioned, larger LDL-C reductions should lead to larger risk reductions (e.g., 60–70% with 3–4 mmol/L LDL-C reductions); however, this is likely only to be clinically relevant in limited circumstances (such as for individuals with familial hypercholesterolemia who have very high LDL-C levels) [25].

High-intensity statin treatment (atorvastatin 80 mg) in the Treating to New Targets (TNT), the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trial and Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, demonstrated an additional 11–23% relative risk reduction of major CVD events, when compared to moderate-intensity statin therapy (atorvastatin 10 mg, simvastatin 20–40 mg, or pravastatin 40 mg). Nonetheless, the atorvastatin 80 mg treated patients still experienced a major CVD event during the trials (ranging from 4 to 11% per year). Mean LDL-C levels in the atorvastatin 80-mg groups ranged from 1.6 to 2.1 mmol/L [26–29].

The American College of Cardiology/American Heart Association 2013 Blood Cholesterol Guideline gives recommendations regarding statin therapy in terms of ASCVD prevention and risk reduction (**Table 1**) [20].

## 2.3 Reductions in coronary mortality

The CTT meta-analyses showed a 12% proportional reduction in vascular mortality per mmol/L LDL-C reduction, attributable to an approximately 20% proportional reduction in coronary deaths, 8% reduction in other cardiac deaths, and little effect on death due to all types of stroke combined. No matter the cause of coronary death, the risk reduction per mmol/L LDL-C reduction appear to be similar in patients with and without pre-existing vascular disease, and in those who present at different levels of baseline vascular risk [22, 23].

ASCVD Statin Benefit Groups [20]			
Heart healthy lifestyle habits are the foundation of ASCVD prevention			
Clinical ASCVD	LDL-C $\geq$ 4.9 mmol/L	Diabetes; age 40–75 years <sup>1</sup>	Estimated 10-yr ASCVD risk $\geq$ 7.5% <sup>2</sup> ; age 40–75 years <sup>1</sup>
<ul style="list-style-type: none"><li>• High-Intensity statin (age <math>\leq</math> 75 years)</li><li>• Moderate-intensity statin if &gt;75 years or not a candidate for high-intensity statin</li></ul>	<ul style="list-style-type: none"><li>• High-intensity statin</li><li>• Moderate-intensity statin if not a candidate for high-intensity statin</li></ul>	<ul style="list-style-type: none"><li>• Moderate-intensity statin</li><li>• High-intensity statin if estimated 10 year ASCVD risk <math>\geq</math> 7.5%</li></ul>	<ul style="list-style-type: none"><li>• Moderate- to high-intensity statin</li></ul>
ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein-cholesterol.			
<sup>1</sup> With LDL-C of 1.8–4.9 mmol/L.			
<sup>2</sup> Estimated using the Pooled Cohort Risk Assessment Equations.			

**Table 1.**  
*Statin therapy in ASCVD prevention and risk reduction according to the 2013 ACC/AHA blood cholesterol guideline.*

Regarding the effect of different statins, and different statin treatment intensities, on coronary mortality, the TNT trial showed no significant differences in the risk of death from cardiovascular or noncardiovascular causes between the patients treated with 10 mg or 80 mg atorvastatin per day [27]. The IDEAL study compared the effects of high-intensity statin therapy (atorvastatin 80 mg/d) vs. low-intensity statin therapy (usual-dose simvastatin, 20 mg/d), on occurrence rates of a major coronary event, defined as coronary death, confirmed nonfatal acute MI, or cardiac arrest with resuscitation. The results failed to show a statistically significant difference in all-cause or cardiovascular mortality between the two treatment regimens [28]. The PROVE-IT trial aimed to compare the effects of 40 mg of pravastatin daily (standard therapy) vs. 80 mg of atorvastatin daily (intensive therapy) in patients hospitalized for acute coronary syndrome. The risk of death due to coronary heart disease, myocardial infarction, or revascularization was reduced by 14% in the atorvastatin group, as compared with 22.3% in the pravastatin group [29].

2.4 The question of residual risk

Despite what was previously elaborated, a significant on-statin treatment residual risk of major CV events still exists. A meta-analysis of statin trials shows that there is residual CVD event risk even with LDL-C levels <2 mmol/L. The aforementioned TNT trial, conducted on patients with stable coronary artery disease (CAD), described an 8.7% incidence of a major event, over 5 years, in patients receiving 80 mg atorvastatin daily, with on-treatment LDL-C concentrations of 1.8–2.6 mmol/L [24]. Findings like these point to the unmet needs of the patients treated with statins. Several cholesterol treatment guidelines recommend a LDL-C treatment goal of <2.6 mmol/L or < 1.8 mmol/L, depending on the level of risk. However, in the everyday clinical practise many high-risk patients fail to reach the goal [26].

The most resent Guidelines, the 2016 European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) Guidelines for the management of Dyslipidemias and The 2017 Guidelines of the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) for Management of Dyslipidemia and Prevention of Cardiovascular Disease have recommended similar target LDL-C levels, and have suggested the use of combination therapy (ezetimibe and PCSK9 inhibitors) to achieve these targets in situations in which maximally tolerated statin monotherapy is insufficient (**Table 2**) [3, 26].

The AACE guidelines introduced an additional “extreme high-risk” category, which is not recognized by the ESC/EAS, and an additional treatment LDL-C target

Risk profile of the patient	Treatment target goal of LDL-C [3]
Very high CV risk	<1.8 mmol/L, or at least 50% reduction if the baseline <sup>3</sup> LDL-C is 1.8–3.5 mmol/L (COR <sup>1</sup> I/LOE <sup>2</sup> B)
High CV risk	<2.6 mmol/L, or at least 50% reduction if the baseline LDL-C is 2.6–5.2 mmol/L (COR I/LOE B)
Low/moderate CV risk	LDL-C goal of <3.0 mmol/L (COR IIa/LOE C)

CV, cardiovascular; LDL-C, low-density lipoprotein-cholesterol.  
<sup>1</sup>COR, class of recommendation.  
<sup>2</sup>LOE, level of evidence.  
<sup>3</sup>“Baseline LDL-C” refers to the LDL-C level in a subject not taking any lipid lowering medication.

**Table 2.**  
*Treatment target goal of LDL-C according to the 2016 ESC/EAS guidelines for the management of dyslipidemias.*

of <1.4 mmol/L. This “extreme high-risk” group represents patients with progressive disease, despite LDL-C levels of <1.8 mmol/L while on-statin therapy. The rationale of the aforementioned approach is in the individualization of the total CV risk reduction, which can be better done if goals are predefined. Treatment goals are defined and tailored to the total CV risk level of each individual patient. The “individualized approach” may possibly result with better patient adherence to the therapy. The growing number of evidence suggests that LDL-C lowering beyond the guidelines-set goals may lead to further reduction of CVD events, which can be especially beneficial in patients at very high CV risk [3, 30].

Given what was previously discussed, in order to achieve this level of LDL-C reduction, combination therapy may be needed. The latest randomized clinical trials (RCTs), such as The LDL-C Assessment With Proprotein Convertase Subtilisin Kexin Type 9 Monoclonal Antibody Inhibition Combined With Statin Therapy 2 (LAPLACE-2) trial, The FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial, and The Reductions in Atherogenic Lipids and Major Cardiovascular Events: A Pooled Analysis of 10 ODYSSEY Trials Comparing Alirocumab With Control, demonstrated that extremely low LDL-C levels (<0.5 mmol/L) appear to be safe. Furthermore, The IMPROVE-IT (Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin vs. Simvastatin) and FOURIER trials demonstrated that not only such low levels are safe, but are also beneficial, in terms of additional CV risk reduction [30–34].

### 3. Combination therapy

#### 3.1 Combination therapy: ezetimibe ad-on statin

The unmet needs in terms of LDL-C targets and ASCVD protection raised the question of statin combination therapy. It only needed to be right positioned. Such positioning was done in the 2016 ESC/EAS Guidelines for the management of Dyslipidemias (Table 3) [3], and also in The 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk [35].

##### 3.1.1 Effects of ezetimibe ad-on statins on LDL-C

The FDA-approved ezetimibe indications are for treatment of primary hyperlipidemia, alone or in combination with a statin; mixed hyperlipidemia in combination



Clinical setting	COR <sup>1</sup> LOE <sup>2</sup>	Treatment target goal of LDL-C	COR <sup>1</sup> LOE <sup>2</sup>
<i>Hypercholesterolemia</i> If the goal is not reached with statins, ad-on ezetimibe	Ia/B	Depends of the risk profile of the individual patient	I/A
<i>FH</i> Intense-dose statin, often in combination with ezetimibe	I/C	<2.6 mmol/L, or <1.8 mmol/L in presence of CVD	Ia/C
<i>ASC</i> If the goal is not reached with the highest tolerable statin dose, ad-on ezetimibe in post-ACS patients	Ia/B	<1.8 mmol/L, or a reduction of at least 50% if the baseline <sup>3</sup> LDL-C is 1.8–3.5 mmol/L	
<i>CKD stages 3–5</i> are high or very high CV risk patients The use of statins or ezetimibe ad-on statin is indicated in non-dialysis dependent patients	I/A	Depends of the risk profile of the individual patient	I/A

*ACS, acute coronary syndrome; FH, familial hypercholesterolemia; CKD, chronic kidney disease; LDL-C, low-density lipoprotein-cholesterol.*  
<sup>1</sup>COR, class of recommendation.  
<sup>2</sup>LOE, level of evidence.  
<sup>3</sup>“baseline LDL-C” refers to the level in a subject not taking any lipid lowering medication.

**Table 3.**  
*Recommendations for ezetimibe add-on statin combination therapy according to the 2016 ESC/EAS guidelines for the management of dyslipidemias.*

with fenofibrates; in homozygote familial hyperlipidemia (HoFH) in combination with atorvastatin or simvastatin; and in homozygous sitosterolemia (phytosterolemia) [3, 26, 35].

In clinical studies, ezetimibe, as monotherapy, reduces LDL-C in hypercholesterolemic patients by 15–22%. Combined therapy with statins provides an incremental reduction in LDL-C levels of 15–20%, leading to a total LDL-C reduction by 34–61%, as previously mentioned [3].

The most comprehensive data analysis for LDL-C lowering efficiency was performed by the group of Descamps, published in 2015. 27 differently designed trials (double-blind placebo and/or active controlled studies), in which statins (type of statin, statin brand, potency or dose difference) were compared with ezetimibe ad-on statin, were included, with over 21,671 patients, analyzing variables such as variances (standard deviation [SD], coefficient of variation [CV], and root mean squared error [RMSE] adjusted for various factors) for % change from baseline in LDL-C. In this very comprehensive data analysis, ezetimibe ad-on statin was found to lead to significantly more pronounced LDL-C lowering, as compared to statin monotherapy [36].

Data from a large retrospective observational study (more than 27,000 patients), published in 2014 by Toth, demonstrated a more pronounced LDL-C lowering effect of ezetimibe ad-on statin therapy, and a higher percentage of goal attainment (with respect to the risk profile of the patients), with one third of the patients not being able to attain the recommended LDL-C goal of <1.8 mmol/L. However, it was realized that there is a low prescription frequency of high-dose statins. Half of the patients (50.9%) remained on the same statin monotherapy, irrespective of their treatment goal achievement [37]. The significance of this study is even bigger given that it is a real life situation, and not a randomized study with strictly predefined inclusion criteria, study population etc.

The IMPROVE-IT study showed an on-trial average LDL-C level of 1.4 mmol/L in the simvastatin-ezetimibe group, as compared to 1.8 mmol/L in the simvastatin-monotherapy group ( $p < 0.001$ ), leading to a total amount of LDL-C reduction of about 24% [38]. There are also a lot of small-scale studies that demonstrate

superiority of ezetimibe ad-on statin therapy in terms of LDL-C lowering. For example, the Japanese study by Uemura, performed on 39 patients, compared two regimens: 10 mg atorvastatin + 10 mg ezetimibe vs. 20 mg atorvastatin in high risk patients with CAD and type 2 diabetes (T2DM). A significant improvement of the lipid profile was found in both groups in terms of total, LDL-C and high-density lipoprotein cholesterol (HDL-C), with a more pronounced improvement in the ezetimibe ad-on atorvastatin group ( $p = 0.005$ ). A significant effect on the Apo B/Apo A-I ratio and remnant-like particle cholesterol was observed only in the atorvastatin ad-on ezetimibe treatment group. Probably the finding that gives as the most powerful information is the effect on oxidized LDL-C [malondialdehyde-modified LDL (MDA-LDL)], a form that is responsible for the proatherogenic effects of LDL-C, that was significantly more pronounced with the atorvastatin ad-on ezetimibe treatment ( $p = 0.0006$ ) [39]. The existence of pleotropic effects, other than the hypo-lipemic effect that is widely recognized for statins, is evidentially true for ezetimibe as well. Evidence of anti-inflammatory and anti-oxidative effects is cumulating. Another Japanese study, by Tobaru, was performed on 35 CAD patients pre-treated with statins who remained above targeted LDL-C level. In terms of hypo-lipemic effect, significant additional decrease of total C, LDL-C, remnant lipoprotein C, LDL/HDL-C ratio was observed, and the percentage of patients who achieved target LDL-C level increased to 65.4% ( $p = 0.001$ ) in the ezetimibe ad-on statin group. Although no significant effect was achieved on high-sensitive C-reactive protein (hsCRP) and oxidative stress markers, a significant reduction of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), 1.36 vs. 0.96 ( $p = 0.042$ ) was observed [40]. On the other hand, given the IMPROVE-IT trial in which two laboratory targets were set: LDL-C ( $<1.8$  mmol/L) and hsCRP ( $<2$  mg/L), Bohula and colleagues summarized that ezetimibe ad-on statin treatment was far more successful in achieving both targets, or it was concluded: "Significantly more patients treated with ezetimibe/simvastatin met prespecified dual LDL-C and hsCRP targets, than patients treated with simvastatin alone (50% vs. 29%,  $p < 0.001$ )". Reaching both LDL-C and hsCRP targets was associated with improved outcomes after multivariable adjustment (38.9% vs. 28.0%, adjusted hazard ratio, 0.73, 0.66–0.81;  $p < 0.001$ ) [38].

### *3.1.2 Effects of ezetimibe ad-on statins on ASCVD outcome*

The potential benefits of adding an additional lipid lowering agent—ezetimibe on statin therapy for CVD prevention and risk reduction have been confirmed in several clinical trials.

The impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: The Multicenter Randomized Controlled PRECISE-IVUS trial evaluated the effects of ezetimibe ad-on atorvastatin vs. atorvastatin monotherapy on the lipid profile and coronary atherosclerosis in Japanese patients who underwent percutaneous coronary intervention (PCI). The combination therapy resulted in lower levels of LDL-C, compared to atorvastatin monotherapy (1.6 mmol/L vs. 1.9 mmol/L;  $p < 0.001$ ), and in the same time coronary plaque regression was observed in significantly higher percentage of patients who received atorvastatin ad-on ezetimibe (78% vs. 58%;  $p = 0.004$ ) [41].

The majority of studies addressing the efficacy of ezetimibe ad-on statin treatment are with simvastatin, including the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study, in patients with aortic stenosis, and the Study of Heart and Renal Protection (SHARP) (Simvastatin plus ezetimibe) trial, including 23% high risk patients with diabetes and chronic kidney disease (CKD) with

or without requiring dialysis. The combination therapy demonstrated superiority over statin monotherapy in LDL-C reduction, translated in reduced primary end-point of first major ASCVD event: nonfatal MI or CV death, non-hemorrhagic stroke, or any arterial revascularization procedure, over a median follow up of 4.9 years [3, 42].

The landmark trial on ezetimibe-statin combination therapy, the largest and the longest one with ezetimibe, is the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). A total of 18,144 patients with acute coronary syndrome (ACS) were randomized to ezetimibe (10 mg) or placebo, all receiving 40 mg simvastatin, which was increased to 80 mg if LDL-C on treatment was  $>2.04$  mmol/L. The event rates for the primary end point at 7 years were 32.7% in the simvastatin-ezetimibe group and 34.7% in the simvastatin-monotherapy group, with an absolute risk reduction of 2% (HR 0.936; 95% CI 0.89–0.99;  $p = 0.016$ ). Ischemic stroke was reduced by 21% ( $p < 0.008$ ). Nevertheless, no benefit in reducing all-cause mortality or deaths from CV causes was observed, which was not unexpected, as prior trials of intensive vs. standard-dose statin therapy did not demonstrate a benefit in terms of mortality as well. There was no evidence of harm caused by the further LDL-C reduction. In this group of patients, already treated with statins to reach the goal, the absolute benefit from the added ezetimibe was small, although significant. However, the study supports the proposition that LDL-C lowering by means other than statins is beneficial and can be performed without adverse effects [38].

The diabetic sub-group analysis in the IMPROVE-IT trial provided the outcomes in 4933 (27%) patients with diabetes, one of the pre-specified trial subgroups. In this patient subset, ezetimibe ad-on statin decreased LDL-C at 1 year by 1.1 mmol/L, as compared to 0.6 mmol/L with statin monotherapy. Diabetic patients on ezetimibe ad-on statin therapy had a 14% relative risk reduction, or 5.5% absolute reduction, compared with a 2% absolute risk reduction for non-diabetics. The most notorious reductions were seen regarding ischemic stroke (39%), MI (24%), and the composite of death due to CV causes, MI or stroke (20%). These CV effects of ezetimibe ad-on statin therapy are considered to be a result of the more prominent reduction of LDL-C (mean 0.5 mmol/L), compared to simvastatin monotherapy, with an average value of 1.4 mmol/L. This sub-study analysis demonstrated superiority of the statin-ezetimibe combination therapy in CV prevention in diabetic subsets especially [26, 34, 35, 38].

Another significant effect of ezetimibe ad-on statin therapy is cerebrovascular protection. The 2013 ACC/AHA cholesterol guideline recommends the use of ezetimibe as an ad-on statin, additional LDL-C lowering agent in stroke patients [35]. The advantage of ezetimibe ad-on statin therapy in this patient subgroup was observed in the IMPROVE-IT study. The highest risk benefit was observed in the subgroup of patients with ischemic CVD with a 21% relative reduction of ischemic stroke ( $p < 0.008$ ). The addition of ezetimibe as a non-statin type drug, to statin treatment contributed to further reduction of LDL-C, which translated into additional decrease in reoccurrence and mortality of/from cerebrovascular events. Achieving target values with ezetimibe ad-on statin combination allows administration of low to moderate-dose statin, which decreases the risks of adverse effects related to high-dose statin therapy [43].

The current trial results make it obvious that the higher the risk profile of the patient is, the bigger is the benefit, in terms of risk reduction, when ezetimibe is ad-on statin treatment. Taken together, all these studies support the decision to propose ezetimibe as a second-line therapy, in association with statins, when the therapeutic goal is not achieved with the maximal tolerated statin dose or in patients intolerant or with contraindications to these drugs [3, 35].



## 3.2 Combination therapy: PCSK9 inhibitors ad-on statin

### 3.2.1 Key points

- The FDA approved the first PCSK9 inhibitor in 2015
- There are currently two PCSK9 inhibitors on the market, alirocumab and evolocumab
- There was a third PCSK9 inhibitor—bococizumab, but its' development was discontinued by Pfizer in late 2016. The key reasons for this were a high level of immunogenicity and wide variability in the LDL-C lowering response.  
*Immunogenicity:* in statin-treated patients, PCSK9 inhibition with bococizumab led to a short-term LDL-C reduction of 55–60%. However, this effect was attenuated over time in 10–15% of patients due to the development of anti-drug antibodies. This effect was specific to bococizumab, which is a partially humanized monoclonal antibody, characterized by substitution of rodent deoxyribonucleic acid (DNA) sequences for <5% of human DNA sequences. It is thought that this substitution may have directly affected the immunogenicity of the antibody. This effect has not been reported for either evolocumab or alirocumab, which are fully human monoclonal antibodies. This immunogenicity may also explain the higher rate of injection site reactions (~10%) observed with bococizumab, compared with either alirocumab or evolocumab (<5%).  
*Variability in LDL-C lowering response:* Irrespective of the presence or absence of antidrug antibodies, there was wide individual variability in the LDL-C lowering response with bococizumab; about 1 in 10 showed no reduction in LDL-C levels
- Patients with familial hyperlipidemia and those with clinical ASCVD, not reaching lipid-reducing goals, including those with statin intolerance, are at greatest need of PCSK9 inhibitors, because no adequate alternative treatment exists
- Multiple guidelines with different approaches to lipid treatment have created confusion among clinicians; thus, defining the patients with ASCVD, or at high CV risk, who have not met LDL-C treatment goals is complicated
- Although PCSK9 inhibitors seem to support the LDL-C hypothesis (the lower the LDL-C level, the lower the CV risk), results of ongoing long-term outcome studies are yet to be presented
- Prescribing PCSK9 inhibitors will likely be limited by economics rather than by clinicians' judgment about the best interest of their patients [44].

Many believe that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are the pharmacotherapeutic innovation of the past 2 decades in terms of CV events prevention.

The 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolemia defined:

*Patients with clinical ASCVD and substantially elevated LDL-C levels* (patients already on maximally tolerated statin therapy (ideally with concomitant ezetimibe), or unable to tolerate three or more statins), and,

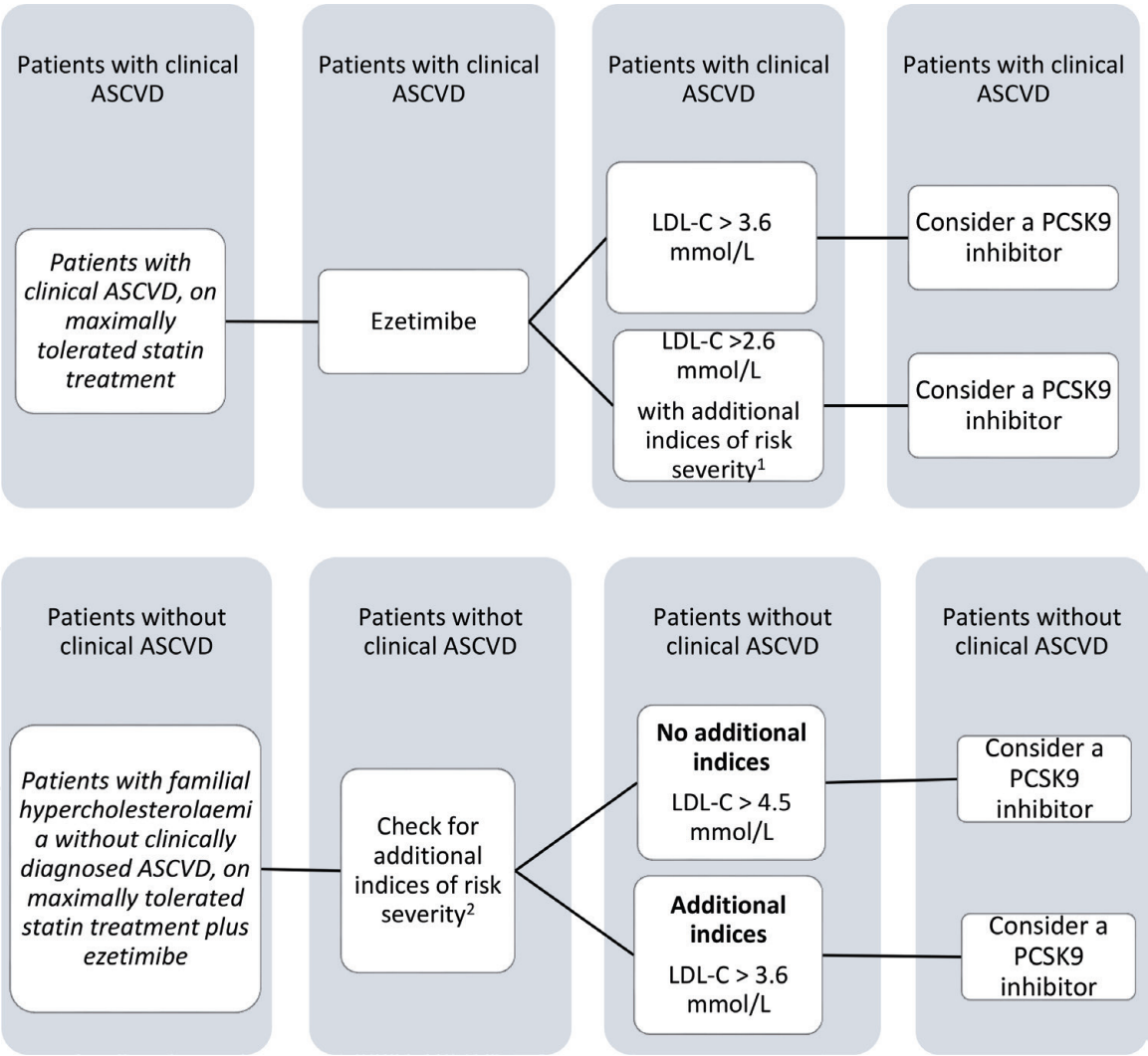


*Familial hypercholesterolemia (FH) patients without clinical ASCVD but with substantially elevated LDL-C levels (patients on maximally tolerated statin therapy plus ezetimibe), as priority patient groups for PCSK9 inhibitors (Figure 1) [45].*

3.2.2 LDL-C lowering and PCSK9 inhibitors: what have we learned?

The Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, aimed to evaluate the efficacy of evolocumab, compared to placebo, in patients with clinically evident CVD. 69% of the patients were on a high-intensity statin, while 30% were on a moderate-intensity statin therapy, randomized to evolocumab 140 mg subcutaneous every 2 weeks or 420 mg monthly (n = 13,784) vs. placebo every 2 weeks (n = 13,780). Evolocumab led to a 59% LDL-C level reduction (from 2.4 mmol/L to 0.78 mmol/L), with an absolute LDL-C reduction of 1.4 mmol/L [46].

The Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-3 (GAUSS-3) trial aimed to evaluate the effect of 24 weeks



**Figure 1.** Appropriate use of PCSK9 inhibitor, as recommended in 2017 update of ESC/ESC task force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolemia. ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein-cholesterol; <sup>1</sup>Including: familial hypercholesterolemia; diabetes mellitus with target organ damage, or a major risk factor; severe and/or extensive ASCVD; rapid progression of ASCVD (i.e. repeated ACS, unplanned coronary revascularizations). <sup>2</sup>Including: diabetes mellitus with target organ damage, or a major risk factor; Lipoprotein(a) > 50 mg/dL; major risk factors: smoking, marked hypertension; >40 years of age without treatment; premature ASCVD (<55 years in males and <60 years in females) in first-degree relatives; imaging indicators.

of evolocumab administered subcutaneously (SC) every month, compared with ezetimibe, on LDL-C levels in adults with high cholesterol, who are unable to tolerate an effective dose of a statin due to muscle-related side effects (MRSE). Evolocumab produced significantly larger reductions in LDL-C levels, compared to ezetimibe (16.7% reduction with ezetimibe and a more than 50% reduction with evolocumab). Despite very high baseline values, the LDL-C goal of less than 1.8 mmol/L was achieved in nearly 30% of evolocumab-treated patients and 1.4% of ezetimibe-treated patients. The LDL-C reduction for both drugs was stable for 4 weeks and sustained during the course of the 24 weeks of treatment [47].

The effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia—the LAPLACE-2 randomized clinical trial evaluated the efficacy and tolerability of evolocumab when used in combination with a moderate- vs. high-intensity statin. 2067 patients with primary hypercholesterolemia and mixed dyslipidemia were randomized to 24 treatment groups. Patients were initially randomized to a daily, moderate-intensity (atorvastatin 10 mg, simvastatin 40 mg, or rosuvastatin 5 mg) or high-intensity (atorvastatin 80 mg, or rosuvastatin 40 mg) statin. After a 4-week lipid-stabilization period, patients were randomized to compare evolocumab (140 mg every 2 weeks) vs. placebo (every 2 weeks) or ezetimibe (10 mg daily; atorvastatin patients only) when added to statin therapies. In patients treated with atorvastatin (10 mg or 80 mg), the addition of ezetimibe resulted in LDL-C reductions by 17–24% from baseline, compared with the addition of evolocumab, administered every 2 weeks, which reduced LDL-C values by 61–62% (treatment differences vs. placebo and ezetimibe both significant [ $p < 0.0001$ ]). For patients receiving a moderate-intensity statin, evolocumab reduced LDL-C values from a baseline mean of 3.1 mmol/L to an on-treatment mean of 1.2 mmol/L, and 88–94% of the patients achieved target LDL-C levels, less than 1.8 mmol/L. For patients receiving a high-intensity statin, evolocumab reduced LDL-C values from a baseline mean of 2.4 mmol/L to an on-treatment mean of 0.9 mmol/L, and 94% achieved the target LDL-C value. In the atorvastatin-treated patients, addition of ezetimibe resulted in achievement of an LDL-C level less than 1.8 mmol/L in 17–20% of patients receiving moderate-intensity statins and 51–62% of those receiving high-intensity statins, vs. 86–94% of patients achieving target LDL-C values in the evolocumab-atorvastatin group [31].

The efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial aimed to compare efficacy, in terms of LDL-C lowering, and safety of alirocumab vs. ezetimibe as ad-on therapy to maximally tolerated statin treatment in high CV risk patients with inadequately controlled hypercholesterolemia. Patients were randomized to subcutaneous alirocumab 75 mg every 2 weeks (plus oral placebo) or oral ezetimibe 10 mg daily (plus subcutaneous placebo) on a background of statin therapy. At week 24, mean  $\pm$  SE reductions in LDL-C from baseline were  $50.6 \pm 1.4\%$  for alirocumab vs.  $20.7 \pm 1.9\%$  for ezetimibe ( $p < 0.0001$ ). 77.0% of alirocumab and 45.6% of ezetimibe patients achieved target LDL-C values of  $<1.8$  mmol/L ( $p < 0.0001$ ). Mean achieved LDL-C levels, by week 24, were 1.3 mmol/L with alirocumab and 2.1 mmol/L with ezetimibe [32].

### *3.2.3 Cardiovascular outcome studies with PCSK9 inhibitors: what have we learned?*

The FOURIER trial, evaluating the effect of evolocumab on the risk of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization, in 27,564 patients with clinically evident CVD, is the first randomized study to be completed, regarding PCSK9 inhibitors long-term efficacy and safety. The primary

outcome, incidence of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization, occurred in 12.6% of the evolocumab group vs. 14.6% of the placebo group ( $p < 0.0001$ ). There was a 9.8% absolute MACE rate reduction, compared to 11.3% with placebo, over 2.2 years, with a relative risk reduction of 15%. This finding was consistent among all tested subgroups. Benefit was enhanced among higher-risk subgroups (those with recent MI, multiple prior MIs, and residual multivessel coronary artery disease), compared to those without such characteristics. There was a linear relationship between LDL-C and adverse CV events, such that adverse events continued to decline to the lowest levels of LDL-C ( $p = 0.0012$ ). Among those with baseline LDL-C  $< 1.8$  mmol/L, evolocumab reduced the primary endpoint (hazard ratio [HR] 0.80, 95% confidence interval [CI] 0.60–1.07) to a similar degree as those with baseline LDL-C  $\geq 1.8$  mmol/L (HR 0.86, 95% CI 0.79–0.92;  $p = 0.65$  for interaction).

There was a greater absolute reduction in major adverse events for evolocumab vs. placebo among those with the highest baseline inflammatory risk (among those with high-sensitivity C-reactive protein  $< 1$  mg/dl, 1–3 mg/dl, and  $> 3$  mg/dl, there was an absolute reduction in the primary outcome of 1.6, 1.8, and 2.7%, respectively). PCSK9 inhibition represents a novel approach to lower LDL-C levels and improves cardiovascular outcomes. However, for the duration of follow-up, there was no benefit on cardiovascular or all-cause mortality, and cost remains an issue [46].

Regarding alirocumab, cardiovascular outcomes and safety will be assessed in an ongoing study, the ODYSSEY Outcomes: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab trial. 18,600 patients, who have experienced an acute coronary syndrome (ACS), are allocated to alirocumab or placebo, for a maximum duration of 64 months. The primary objective of the trial is to compare the effect of alirocumab with placebo on the occurrence of cardiovascular events (composite endpoint of coronary heart disease (CHD) death, non-fatal MI, fatal and non-fatal IS, unstable angina requiring hospitalization). No results are reported yet [32].

## **4. Safety profiles of statin monotherapy and statin combination therapy**

### **4.1 Adverse effects of statin therapy**

The only excesses of adverse events that have been reliably demonstrated to be caused by statin therapy are myopathy and diabetes mellitus, along with a probable excess of hemorrhagic stroke. However, the absolute risks of these adverse effects remain small, by comparison with the absolute benefits [25].

#### *4.1.1 Increases in myopathy rates*

Approved statin regimens have been associated, both in observational studies and in randomized trials, with large relative risks for myopathy, but typically with small absolute excesses (about 1 case per 10,000 people treated per year), and even smaller excesses in the incidence of rhabdomyolysis (about 2–3 cases per 100,000 treated per year). It usually resolves rapidly when statin therapy is . [48]. The risk of myopathy is dose related and it appears to depend on the statin circulation levels. In the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) randomized trial, simvastatin 80 mg daily produced a more than ten-fold higher rate (at least 1 case of myopathy per 1000 patients treated yearly), compared to 20 mg daily (about 1 case per 10,000 yearly), so the high-dose regimen is no longer recommended routinely [49].



#### *4.1.2 Increases in diabetes rates*

In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) randomized trial, among 17,802 patients without a history of vascular disease, concentrations of glycated hemoglobin, after 2 years, were slightly higher among the patients allocated to rosuvastatin 20 mg daily compared to those allocated to placebo (5.9 vs. 5.8%;  $p = 0.001$ ). There was also a small excess of newly diagnosed diabetes (3.0 vs. 2.4%;  $p = 0.01$ ), which corresponds to a 25% proportional increase. In subsequent meta-analyses, standard statin dose regimens were associated with a proportional increase of about 10% in reported diabetes, and more intensive statin regimens (as used in JUPITER) with about a 10% further increase. This excess of diabetes diagnoses appeared soon after the start of statin therapy, mainly among patients who had previous risk factors for diabetes [50].

#### *4.1.3 Probable increases in hemorrhagic stroke rates*

In The Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) trial, among 4731 patients with prior cerebrovascular disease, allocation to atorvastatin 80 mg daily produced a definite reduction in ischemic stroke (218 [9.2%] vs. 274 [11.6%];  $p = 0.008$ ), but there was also a possible increase in hemorrhagic stroke (55 [2.3%] vs. 33 [1.4%];  $p = 0.02$ ). When these results were combined with those from the other trials included in the CTT meta-analysis, there was a 21% (95% CI 5–41;  $p = 0.01$ ) proportional increase in the incidence of hemorrhagic stroke per mmol/L reduction in LDL-C [51].

### **4.2 Safety profile of ezetimibe ad-on statins combination therapy**

The relationship between lipid-lowering medications, glycemic control, insulin resistance and new-onset diabetes has been studied since the introduction of hypo-lipemic medications. We know that glycemic control is impaired not only by statin treatment but also with niacin. At the opposite, bile-acid sequestrates demonstrate moderate lipid and glucose lowering effects, and fibrates (particularly bezafibrate) may produce beneficial effects on glucose metabolism and insulin sensitivity. Considering statins, as the most widely used hypo-lipemic drugs, this is an important issue. Statins lead to a mild elevation of hemoglobin A1c (HgbA1c) and fasting plasma glucose (FPG), and increase the incidence of new-onset diabetes, an effect known to be dose and agent dependent (Pravastatin and Pitavastatin have less diabetogenic effect and positive impact on insulin sensitivity). The aforementioned is most pronounced in patients with baseline impaired fasting blood glucose (FBG), at older age and with metabolic syndrome. However, it has been demonstrated that the risk of new-onset diabetes is outweighed by the benefit of CV risk reduction [3].

For a long period of time there was a lack of clinical trials addressing the same question in ezetimibe treatment, but data was gathered from experimental animal studies that described how ezetimibe ameliorates metabolic markers, such as hepatic steatosis and insulin resistance. The process is via inhibition of the intestinal cholesterol absorption, and inhibition of the hepatic NPC1L1, leading to decreased hepatic insulin resistance, improved glycemic control and insulin sensitivity, especially in patients with metabolic disorders (obesity and hepatic steatosis). This was harder to prove in humans, as ezetimibe is usually used as statin co-therapy and individual impact of ezetimibe cannot be evaluated. In a recently published systematic review of randomized clinical trials, performed by Wu



and co-authors on 2440 patients, experimental data was confirmed. Ezetimibe did not cause any adverse effects in terms of increased levels of FBG and HbA1c. Compared with high-dose statin therapy, ezetimibe ad-on low-dose statin for more than 3 months may even have beneficial effects on glycemic control [52].

Statin associated muscle symptoms are a very common side effect, also known to be dose-dependent. It seems that ezetimibe ad-on low dose statin therapy is one of the possibilities to achieve good LDL-C control and CV risk reduction with lesser side effects, as demonstrated with myalgia [53]. The 2016 ESC/EAS Guidelines for the management of dyslipidemias recommend ezetimibe to be considered in combination with a low-dose statin or second- or third-line statin in order to manage statin-attributed muscle symptoms [3].

#### **4.3 Safety profile of PCSK9 inhibitors ad-on statins combination therapy**

Despite this new evidence from the FOURIER trial, gaps remain in our knowledge regarding the use of PCSK9 inhibition in clinical practice. The ODYSSEY Outcomes trial will provide additional information in patients treated with a PCSK9 inhibitor within 1–12 months [45].

As with all novel treatments, long-term safety remains to be established. To date there are exposure data for up to 4 years' treatment with a PCSK9 inhibitor, involving a background of concomitant statin therapy. Potential injection site reactions occurred in <5% of patients, and were mainly of very mild intensity with no evidence of a cumulative effect. When the PCSK9 inhibitor was compared to the previous standard of care (statin with or without ezetimibe), annualized event rates for muscle symptoms (4.7% vs. 8.5% with standard of care), and new-onset diabetes (2.8% vs. 4.0%, respectively) appeared similar [45].

The safety of very low LDL-C levels merits special consideration, given that one in four patients treated with evolocumab in FOURIER attained LDL-C levels less than 0.5 mmol/L. Evidence to date suggests no detrimental impact on steroid hormone production, enterohepatic circulation of bile acids, or neuronal cell function. Indeed, these LDL-C levels are also consistent with the very low levels observed in newborns which, despite the physiological and developmental demands of infancy, are compatible with normal development [54].

Additionally, data from the ODYSSEY program, the FOURIER and 6-year follow-up from the IMPROVE-IT trial showed no increase in adverse events including severe muscle symptoms, liver enzyme elevation, cognitive adverse events, or hemorrhagic stroke with very low LDL-C levels [45].

### **5. The war of today**

We now know the battle is going to be very hard. The “old ones” are not ready to go to history, while the “young ones” are still to be proven. What does the newest published data say? In January 2018 Khan and co-authors published a meta-analysis of statins, PCSK9 inhibitors and ezetimibe, the later two with or without statins, regarding ASCVD reduction benefit. The most comprehensive meta-analysis included 189,116 patients from 39 randomized control trials. PCSK9 inhibitors were ranked as the best treatment for prevention of major adverse cardiovascular events: myocardial infarction and stroke. Statins were ranked as the most effective therapy for reducing all-cause and CV mortality. In terms of reduction of CV mortality PCSK9 inhibitors were ranked as the second best treatment followed by ezetimibe ad-on statin [55].

6. Conclusion

Statins remain the cornerstone anti-lipemic treatment, proven to be very effective in reducing ASCVD risk. Ezetimibe ad-on statin combination therapy is an effective treatment that leads to additional LDL-C lowering, recommended in situations where with maximal or maximally tolerated statin monotherapy treatment LDL-C target goals cannot be achieved. It leads to an additional CVD risk reduction, and in the same time is safe, with a possible beneficial effect over the statin adverse influence on glycemic metabolism. Having in mind the evidence from the first of the cardiovascular outcomes studies with PCSK9 inhibitors, the addition of a PCSK9 inhibitor should be considered in patients with ASCVD, and in FH patients without a prior clinical event, who have substantially elevated LDL-C levels despite maximally tolerated statin with or without ezetimibe therapy, or inability to tolerate appropriate doses of at least three statins. Prioritizing the use of combination therapy in these specific patient groups may help reduce cardiovascular outcomes and the impact of the associated physical and/or psychological disability.

Acknowledgements

Both authors equally contributed to this chapter.

Conflict of interest

We declare no conflict of interest. This chapter was written independently. No company or institution supported it financially.

Abbreviations

AACE	American Association of Clinical Endocrinologists
ABC	ATP-binding cassette
ACC/AHA	American College of Cardiology/American Heart Association
ACE	American College of Endocrinology
ACS	acute coronary syndrome
ApoB	apolipoprotein B
ARIC study	the Atherosclerosis Risk in Communities study
ASCVD	atherosclerotic cardiovascular disease
CAD	coronary artery disease
CHD	coronary heart disease
CKD	chronic kidney disease
CTT	Cholesterol Treatment Trialists' Collaboration
CV	cardiovascular
CV	coefficient of variation
CVD	cardiovascular disease
CYP450	cytochrome P450
DNA	deoxyribonucleic acid
ESC/EAS	European Society of Cardiology/European Atherosclerosis Society
FBG	fasting blood glucose
FDA	Food and Drug Administration
FH	familial hypercholesterolemia

FOURIER trial	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk trial
FPG	fasting plasma glucose
GAUSS-3 trial	the Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-3 trial
HDL-C	high-density lipoprotein cholesterol
HgBA1C	hemoglobin A1c
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HoFH	homozygote familial hyperlipidemia
hsCRP	high-sensitive C-reactive protein
IDEAL trial	the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering trial
IDL	intermediate density lipoproteins
IgG1	immunoglobulin G1
IMPROVE-IT study	Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin vs. Simvastatin
IS	ischemic stroke
JUPITER trial	in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin randomized trial
LAPLACE-2 trial	the LDL-C Assessment With Proprotein Convertase Subtilisin Kexin Type 9 Monoclonal Antibody Inhibition Combined With Statin Therapy 2 trial
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LDL-R	LDL receptor
Lp(a)	lipoprotein(a)
MDA-LDL	malondialdehyde-modified LDL
MI	myocardial infarction
MoAbs	monoclonal antibodies
MRSE	muscle-related side effects
MVE	major vascular events
NPC1L1	Niemann Pick C1 like 1 protein
ODDYSEY trial	the Reductions in Atherogenic Lipids and Major Cardiovascular Events: A Pooled Analysis of 10 ODYSEY Trials Comparing Alirocumab With Control
PCI	percutaneous coronary intervention
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
PRECISE-IVUS trial	the Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention: The Multicenter Randomized Controlled trial
PROVE-IT trial	Pravastatin or Atorvastatin Evaluation and Infection Therapy trial
RCTs	randomized clinical trials
RMSE	root mean squared error
SC	subcutaneously
SD	standard deviation
SEARCH trial	in the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine randomized trial
SEASE study	Simvastatin and Ezetimibe in Aortic Stenosis study
SHARP trial	the Study of Heart and Renal Protection (Simvastatin plus ezetimibe) trial

SLC	solute carrier
SPARCL trial	in The Stroke Prevention by Aggressive Reduction of Cholesterol Levels trial
T2DM	type 2 diabetes mellitus
TNF- $\alpha$	tumor necrosis factor- $\alpha$
TNT trial	treating to New Targets trial
UGT	UDP-glucuronosyltransferase
VLDL	very low-density lipoproteins

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## References

- [1] 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 European Atherosclerosis Society Consensus Panel. *European Heart Journal*. 2017;**38**(32):2459-2472. DOI: 10.1093/eurheartj/ehx144
- [2] Nozue T. Lipid lowering therapy and circulating PCSK9 concentration. *Journal of Atherosclerosis and Thrombosis*. 2017;**24**(9):895-907. DOI: 10.5551/jat.RV17012
- [3] Catapano AL, Graham I, De Backer G, et al. The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *European Heart Journal*. 2016;**37**:2999-3058. DOI: 10.1093/eurheartj/ehw272
- [4] Robinson JG. Nonstatins and Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors: Role in non-familial hypercholesterolemia. *Progress in Cardiovascular Diseases*. 2016;**59**(2):165-171. DOI: 10.1016/j.pcad.2016.07.009
- [5] Ramkumar S, Raghunath A, Raghunath S. Statin therapy: Review of safety and potential side effects. *Acta Cardiologica Sinica*. 2016;**32**(6):631-639. DOI: 10.6515/ACS20160611A
- [6] McFarland AJ, Anoopkumar-Dukie S, Arora DS, et al. Molecular mechanisms underlying the effects of statins in the central nervous system. Harry GJ, ed. *International Journal of Molecular Sciences*. 2014;**15**(11):20607-20637. DOI: 10.3390/ijms151120607
- [7] Gazzerri P, Proto MC, Gangemi G, et al. Pharmacological actions of statins: A critical appraisal in the management of cancer. *Pharmacological Reviews*. 2012;**64**(1):102-146. DOI: 10.1124/pr.111.004994
- [8] Meor Anuar Shuhaili MFR, Samsudin IN, Stanslas J, et al. Effects of different types of statins on lipid profile: A perspective on Asians. *International Journal of Endocrinology and Metabolism*. 2017;**15**(2):e43319. DOI: 10.5812/ijem.43319
- [9] Smith BA, Wright C, Davidson M. Role of Ezetimibe in lipid-lowering and cardiovascular disease prevention. *Current Atherosclerosis Reports*. 2015;**17**:72. DOI: 10.1007/s11883-015-0550-5
- [10] Hammersley D, Signy M. Ezetimibe: An update on its clinical usefulness in specific patient groups. *Therapeutic Advances in Chronic Disease*. 2017;**8**(1):4-11. DOI: 10.1177/2040622316672544
- [11] Tie C, Gao K, Zhang N, et al. Ezetimibe attenuates atherosclerosis associated with lipid reduction and inflammation inhibition. *PLoS One*. 2015;**10**(11):e0142430. DOI: 10.1371/journal.pone.0142430
- [12] Kim H, Choi HY, Kim YH, et al. Pharmacokinetic interactions and tolerability of rosuvastatin and ezetimibe: An open-label, randomized, multiple-dose, crossover study in healthy male volunteers. *Drug Design, Development and Therapy*. 2018;**12**:815-821. DOI: 10.2147/DDDT.S158408
- [13] Nabil GS. Proprotein Convertase Subtilisin Kexin 9 (PCSK9) inhibitors in the treatment of

hypercholesterolemia and other pathologies. *Current Pharmaceutical Design*. 2013;**19**:3161-3172. DOI: 10.2174/13816128113199990313

[14] Page MM, Watts GF. PCSK9 inhibitors—Mechanisms of action. *Australian Prescriber*. 2016;**39**(5):164-167. DOI: 10.18773/austprescr.2016.060

[15] Giugliano RP, Sabatine MS. Are PCSK9 inhibitors the next breakthrough in the cardiovascular field? *Journal of the American College of Cardiology*. 2015;**65**(24):2638-2651. DOI: 10.1016/j.jacc.2015.05.001

[16] Hess PL, Kennedy K, Cowherd M, et al. Implications of the FDA approval of PCSK9 inhibitors and FOURIER results for contemporary cardiovascular practice: An NCDR research to practice (R2P) project. *American Heart Journal*. 2018;**195**:151-152. DOI: 10.1016/j.ahj.2017.09.004

[17] Fala L. Repatha (Evolocumab): Second PCSK9 inhibitor approved by the FDA for patients with familial hypercholesterolemia. *American Health & Drug Benefits*. 2016;**9** (Spec Feature):136-139

[18] Manniello M, Pisano M. Alirocumab (Praluent): First in the new class of PCSK9 inhibitors. *Pharmacy and Therapeutics*. 2016;**41**(1):28-53

[19] Carroll MD, Kit BK, Lacher DA, Shero ST, Mussolino ME. Trends in lipids and lipoproteins in US adults, 1988-2010. *Journal of the American Medical Association*. 2012;**308**:1545-1554

[20] Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;**129** (suppl 2):S1-S45

[21] Soran H, Schofield JD, Durrington PN. Cholesterol, not just cardiovascular risk, is important in deciding who should receive statin treatment. *European Heart Journal*. 2015;**36**:2975-2983

[22] Cholesterol Treatment Trialists' (CTT) Collaboration. 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

[23] Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: Meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;**380**:581-590

[24] Soran H, Dent R, Durrington P. Evidence-based goals in LDL-C reduction. *Clinical Research in Cardiology*. 2017;**106**:237-248. DOI: 10.1007/s00392-016-1069-7

[25] Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet*. 2016;**388**:2532-2561. DOI: 10.1016/S0140-6736(16)31357-5

[26] Jellinger PS, Handelsman Y, Rosenblit PD, et al. AACE 2017 Guidelines, American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. *Endocrine Practice*. 2017;**23**(Suppl 2):1-63

[27] LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *The New England Journal of Medicine*. 2005;**352**:1425-1435. DOI: 10.1056/NEJMoa050461

[28] Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose

atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction the IDEAL study: A randomized controlled trial. *Journal of the American Medical Association*. 2005;**294**(19):2437-2445. DOI: 10.1001/jama.294.19.2437

[29] Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *The New England Journal of Medicine*. 2004;**350**:1495-1504. DOI: 10.1056/NEJMoa040583

[30] Baer J. AACE and EAS lipid guidelines. Expert analysis. AACE and EAS lipid guidelines—American College of Cardiology [internet]. <http://www.acc.org/latest-in-cardiology/articles/2017/08/11/08/35/aace-and-eas-lipid-guidelines>. [Accessed: 2018-10-05]

[31] Robinson JG, Rogers WJ, Nedergaard BS, et al. Rationale and design of LAPLACE-2: A phase 3, randomized, double-blind, placebo- and Ezetimibe-controlled trial evaluating the efficacy and safety of Evolocumab in subjects with hypercholesterolemia on background statin therapy. *Clinical Cardiology*. 2014;**37**(4):195-203. DOI: 10.1002/clc.22252

[32] Ray KK, Ginsberg HN, Davidson MH, et al. Reductions in atherogenic lipids and major cardiovascular events: A pooled analysis of 10 ODYSSEY trials comparing alirocumab with control. *Circulation*. 2016;**134**(24):1931-1943. DOI: 10.1161/CIRCULATIONAHA.116.024604

[33] Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *The New England Journal of Medicine*. 2017;**376**(1713):1722. DOI: 10.1056/NEJMoa1615664

[34] Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin

therapy after acute coronary syndromes. *The New England Journal of Medicine*. 2015;**372**(2387):2397. DOI: 10.1056/NEJMoa1410489

[35] Lloyd-Jones D, Morris P, Ballantyne C, et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *Journal of the American College of Cardiology*. 2016;**68**:92-125. DOI: 10.1016/j.jacc.2016.03.519

[36] Descamps O, Tomassini JE, Lin J, et al. Variability of the LDL-C lowering response to ezetimibe and ezetimibe + statin therapy in hypercholesterolemic patients. *Atherosclerosis*. 2015;**240**(2):482-489. DOI: 10.1016/j.atherosclerosis.2015.03.004

[37] Toth PP, Foody JM, Tomassini JE, et al. Therapeutic practice patterns related to statin potency and ezetimibe/simvastatin combination therapies in lowering LDL-C in patients with high-risk cardiovascular disease. *Journal of Clinical Lipidology*. 2014;**8**(1):107-116. DOI: 10.1016/j.jacl.2013.09.009

[38] Bohula E, Giugliano R, Cannon C, et al. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. *Circulation*. 2015;**132**:1224-1233. DOI: 10.1161/CIRCULATIONAHA.115.018381

[39] Uemura Y, Watarai M, Ishii H, et al. Atorvastatin 10 mg plus ezetimibe 10 mg compared with atorvastatin 20 mg: Impact on the lipid profile in Japanese patients with abnormal glucose tolerance and coronary artery disease. *Journal of Cardiology*. 2012;**59**(1):50-56. DOI: 10.1016/j.jjcc.2011.09.001



- [40] Tobaru T, Seki A, Asano R, et al. Lipid-lowering and anti-inflammatory effect of ezetimibe in hyperlipidemic patients with coronary artery disease. *Heart and Vessels*. 2013;**28**(1):39-45. DOI: 10.1007/s00380-012-0243-8
- [41] Tsujita K, Sugiyama S, Sumida H, et al. Impact of dual lipid-lowering strategy with Ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: The multicenter randomized controlled PRECISE-IVUS trial. *Journal of the American College of Cardiology*. 2015;**66**(5):495-507. DOI: 10.1016/j.jacc.2015.05.065
- [42] Mancini J, Hegele R, Leiter L. Dyslipidemia. Canadian Diabetes Association clinical practice guidelines expert committee. *Canadian Journal of Diabetes*. 2013;**37**(Suppl 1):S110-S116. DOI: 10.1016/j.cjcd.2013.01.032
- [43] Lovadi E, Csécséi P, Lovig C, et al. Lipids and cerebrovascular disease—New therapeutic options in lowering LDL-cholesterol. *Orvosi Hetilap*. 2016;**157**(52):2059-2065. DOI: 10.1556/650.2016.30643
- [44] Lepor NE, Kereiakes DJ. The PCSK9 inhibitors: A novel therapeutic target enters clinical practice. *American Health & Drug Benefits*. 2015;**8**(9):483-489
- [45] Landmesser U, Chapman MJ, Stock JK, et al. 2017 update of ESC/EAS task force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia. *European Heart Journal*. 2017;**0**:1-13
- [46] Sabatine MS, Giugliano RP, Keech AC, et al. FOURIER steering committee and investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *The New England Journal of Medicine*. 2017;**376**:1713-1722
- [47] Nissen SE, Stroes E, Dent-Acosta R, et al. Efficacy and tolerability of Evolocumab vs Ezetimibe in patients with muscle-related statin IntoleranceThe GAUSS-3 randomized clinical trial. *Journal of the American Medical Association*. 2016;**315**(15):1580-1590. DOI: 10.1001/jama.2016.3608
- [48] Macedo AF, Taylor FC, Casas JP, et al. Unintended effects of statins from observational studies in the general population: Systematic review and meta-analysis. *BMC Medicine*. 2014;**12**:51
- [49] SEARCH Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: A double-blind randomised trial. *Lancet*. 2010;**376**:1658-1669
- [50] Ridker PM. The JUPITER Trial—results, controversies, and implications for prevention. *Circulation: Cardiovascular Quality and Outcomes*. 2009;**2**:279-285
- [51] Huisa BN, Stemmer AB, Zivin JA. Atorvastatin in stroke: A review of SPARCL and subgroup analysis. *Vascular Health and Risk Management*. 2010;**6**:229-236
- [52] Wu H, Shang H, Wu J. Effect of ezetimibe on glycemic control: A systematic review and meta-analysis of randomized controlled trials. *Endocrine*. 2018;**60**(2):229-239. DOI: 10.1007/s12020-018-1541-4
- [53] Saxon DR, Eckel RH. Statin intolerance: A literature review and management strategies. *Progress in Cardiovascular Diseases*. 2016;**59**(2):153-164. DOI: 10.1016/j.pcad.2016.07.009
- [54] Olsson AG, Angelin B, Assmann G, et al. Can LDL cholesterol be too low? Possible risks of extremely low levels. *Journal of Internal Medicine*. 2017;**281**:534-553



[55] Khan SU, Talluri S, Riaz H, et al.  
A Bayesian network meta-analysis  
of PCSK9 inhibitors, statins and  
ezetimibe with or without statins  
for cardiovascular outcomes.  
European Journal of Preventive  
Cardiology. 2018;25(8):844-853. DOI:  
10.1177/2047487318766612

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