


**Review Article**

## Pleiotropic Effects of Statins-What is their Clinical Significance?

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### Abstract

Pleiotropic effects are effects not related to the primary effect of drugs. Statins, beside their primary effect, which is LDL-lowering, have several pleiotropic effects, such as anti-inflammation, anti-thrombotic effects, inhibition of smooth muscle cell proliferation and apoptosis, inhibition of migration and activation of macrophages. They increase blood glucose with the exception of pitavastatin. The clinical importance of these pleiotropic effects of statins however remains unclear. No matter of whether LDL-lowering was done by statins or by other means, the lowering of the cardiovascular risk is the same. The reduction in LDL-C per se is responsible for the beneficial effect. However, pleiotropic effects of statins might play a role with respect to micro vascular events. The difference in pleiotropic effects between the different statins might be a basis for a patient-oriented statin therapy.

**Keywords:** Statins; Pleiotropic effects; LDL cholesterol; Cardiovascular events; Personalized statin therapy

### Introduction

Pleiotropic effects refer to the effects of drugs that are not directly related to their primary effect. In the case of statins, these are the effects that are not directly related to the lowering of Low-Density Lipoprotein Cholesterol (LDL-C). Statins apart from their lipid lowering have effects on inflammation, thrombosis, proliferation of smooth muscle and apoptosis. Interest in these effects of statins has waned in recent years. Due to new guidelines which recommend much lower target values for patients with high cardiovascular risk [1]. This has led to the use of combinations of drugs as it is already the case of antihypertensive drugs. They may consist of statins plus ezetimibe or statins plus PCSK9 inhibitors or a combination of all three drugs. These combinations have shown an additional benefit by the more intensive cholesterol lowering [2, 3]. The LDL cholesterol lowering of different drugs and their combinations is shown in (Table 1).

**Table 1:** Treatment intensity and effect on LDL cholesterol [1].

Treatment modality	Mean LDL cholesterol reduction
Moderate intensity of statin	Ca. 30%
High intensity of statin	Ca. 50%
High intensity of statin plus ezetimibe	Ca. 65%
PCSK9 inhibitor	Ca. 60%
PCSK9 inhibitor plus high intensity statin	Ca. 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	Ca. 85%

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## Pharmacokinetics of statins

The rate-limiting enzyme in cholesterol biosynthesis in the liver is HMG-CoA reductase, which catalyzes the conversion of HMG-CoA to mevalonic acid. Statins work by reversibly inhibiting HMG-CoA reductase, thus reducing hepatic cholesterol synthesis, up regulation of LDL receptors and increased hepatic uptake of LDL-cholesterol from the circulation.

## Cholesterol synthesis can be divided into three steps

**Synthesis of activated isoprene units:** From acetyl-CoA, the activated isoprene units 3-isopentenyl pyrophosphate and 3,3-dimethylallyl pyrophosphate are formed via acetoacetyl-CoA, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) and mevalonate.

**Condensation of activated isoprene units to squalene:** Six activated isoprene units (four isopentenyl pyrophosphate and two dimethylallyl pyrophosphate) form squalene via the intermediates geranyl pyrophosphate and farnesyl pyrophosphate.

**Cyclisation of squalene and conversion to cholesterol:** Squalene is subsequently cyclised via squalene epoxide to lanosterol, which is converted to cholesterol in numerous further rearrangements and excretions.

Inhibition of isoprenoid synthesis and the associated disruption of Ras, Rho, CDC42 and Rac signalling has a positive effect on the vascular endothelium by reducing oxidative stress and activating anti-inflammatory and anti-proliferative mechanisms. These effects are essentially responsible for the pleiotropic activities of statins. They are independent of cholesterol synthesis and act quickly, in contrast to cholesterol inhibition and the associated LDL cholesterol reduction, which act rather slowly and only become clinically effective after years, as was shown for the first time in the 4S study [4].

## Statins exert various pleiotropic effects

The main pleiotropic effects of statins are effects on cell function and division, effects on oxidative processes, anti-inflammatory effects, effects on coagulation and on vasomotor activity, and an increase in glucose concentration with the potential risk of diabetes, which is an adverse effect. These effects vary between the different statins. All statins have an anti-inflammatory effect, but there are quantitative differences. The lipophilic statins atorvastatin, simvastatin, rosuvastatin and pitavastatin have an antithrombotic effect, the hydrophilic pravastatin does not. The statins do not differ with respect to platelet aggregation, but smooth muscle cell proliferation and apoptosis are favoured only by the lipophilic statins; pravastatin has no effect on smooth muscle cell proliferation and apoptosis. The blood-brain

passage is passed by atorvastatin and simvastatin, but not by pravastatin, fluvastatin, rosuvastatin and pitavastatin. These effects depend largely on the lipophilicity of the statins and on their metabolism via the cytochrome P450 system. Lipophilic statins are atorvastatin (metabolised by CYP 450 3A4), simvastatin (metabolised by CYP 450 3A4), pitavastatin (minimally metabolised by CYP450 2C9). Hydrophilic statins are pravastatin (minimally metabolised by the CYP450 system), rosuvastatin (barely metabolised by CYP450) and fluvastatin (metabolised by CYP450 2C9). All statins, especially at high doses, are associated with an increase in blood glucose and HbA1c [5, 6]. The only statin that has no effect on blood glucose is pitavastatin [7]. However, the beneficial effects of statin therapy outweigh its potential harms in diabetes, with a NNH (Number Needed to Harm) of 498 versus a NNT (Number Needed to Treat) of 155 [8].

## Personalised statin therapy

The differences between statins in terms of their pleiotropic effects and adverse side effects point to the benefits of personalised statin therapy. In this context, certain statins should be favoured in certain situations. In patients with prediabetes or the metabolic syndrome, pitavastatin may be preferred as this statin has been shown to have no effect on blood glucose or HbA1c levels [7]. One of the best-known adverse effects of statins is muscle problems, which occur in about 20% of statin users in the real world and in about 2% in statin clinical trials. Fluvastatin has been shown in the PRIMO trial [9] to have fewer effects on muscle symptoms than other statins. Combining a statin with ezetimibe has been shown to be beneficial in older people, a population often thought to benefit less from statin therapy. Ouchi and colleagues have shown in the EWTOPIA study that older people can benefit from combining statins with ezetimibe [10]. In the case of statin intolerance, often due to muscle pains bempedoic acid eventually combined with ezetimibe may be used [11]. Bempedoic acid is a prodrug. In the organism, activation by the very long-chain acyl-CoA synthetase (ACSLV1) produces the biologically active bempedoic acid-CoA, which competitively inhibits ATP Citrate Lyase (ACL). ACL is an enzyme of energy metabolism in all eukaryotes. ACSLV1 is mainly found in the liver, but not in skeletal muscle. Thus muscle pain, one of the major undesired side effects of statins does not occur with bempedoic acid.

## Are pleiotropic effects clinically relevant ?

A log-linear association per unit change in low-density lipoprotein cholesterol and the risk of cardiovascular disease has been reported in meta-analyses of Mendelian randomization studies, prospective epidemiologic cohort studies, and randomized trials. The increasingly steeper slope of the log-linear association with increasing length of follow-up time implies that LDL-C has both a causal and a

cumulative effect on the risk of cardiovascular disease. This log-linear relationship was maintained regardless of whether LDL-lowering was achieved by statins or other lipid-lowering measures. Thus the results of the IMPROVE-IT study with ezetimibe on top of simvastatin were exactly on the same curve as the effects with statin alone [12]. Similar data were shown in the FOURIER Study [2] with evolocumab on top of statins and in the ODYSSEY OUTCOME study (3) with alirocumab. No matter how the LDL-cholesterol reduction was achieved the relationship between LDL cholesterol lowering and the reduction in cardiovascular events remained constant and the distinct point were on the same line. This indicates that it is the LDL cholesterol lowering per se which leads to the reduction in cardiovascular events and this depends on the intensity of LDL-lowering and the time of exposure to LDL cholesterol [13].

### Key messages

Statins have several beneficial pleiotropic effects, most notably anti-inflammatory and anti-coagulant effects, inhibition of smooth muscle cell proliferation and apoptosis, and inhibition of macrophage migration and activation.

Statins, especially in high doses, also increase blood glucose and HbA1c. However, the beneficial effect on cardiovascular events far outweighs any possible harm.

The beneficial effects on cardiovascular endpoints, however, are largely independent of the pleiotropic effects.

The reduction of cardiovascular events is largely due to the LDL cholesterol reduction per se.

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