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# The benefits of statin therapy outweigh their side effects

## Koristi zdravljenja s statini odtehtajo njihove stranske učinke

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## Abstract

Statins have been among the most commonly prescribed drugs in more than twenty years. By reducing LDL cholesterol, drugs from this group significantly reduce cardiovascular morbidity and mortality. Statins competitively inhibit the active site of the first and critical rate-limiting enzyme in the mevalonate pathway, HMG-CoA reductase. In addition to the effects on lowering LDL cholesterol, their mechanism of action is also responsible for most of the side effects. However, we do not have reliable data for that statement. The most common side effects, which are also the reason for discontinuing statin treatment, are related to muscle pain. The exact extent of the muscle adverse effects is not known, as we do not have a uniform definition of these side effects. Other side effects include newly onset of type 2 diabetes, hepatotoxicity, haemorrhagic stroke, and neurological disorders. Despite all these side effects, the benefits of statin treatment far outweigh these side effects. Despite new therapies to lower LDL cholesterol and thus reduce cardiovascular mortality, statin therapy will remain the first choice in both primary and secondary prevention for the next few years. The main drawback of the new therapies is that we do not have enough data on their long-term efficacy and safety. In any case, we should not neglect the economic aspect either, as the cost-effectiveness of statins is much higher compared to new drugs.

## Izvleček

Zdravila iz skupine statinov so v zadnjih več kot 20 letih ena najpogosteje predpisovanih zdravil. Poleg znižanja koncentracije holesterola LDL namreč zelo pomembno znižajo srčnožilno obolevnost in umrljivost. Statini kompetitivno zavirajo aktivno mesto reduktaze HMG-CoA prvega in ključnega hitrost omejujočega encima v mevalonatni poti. Ta mehanizem je poleg zmanjšanja vrednosti holesterola LDL najverjetneje odgovoren tudi za večino stranskih učinkov, čeprav za to ni zanesljivih dokazov. Najpogostejši stranski učinki, ki so tudi vzrok za prekinitev zdravljenja, so povezani z mišičnimi bolečinami, čeprav natančne razširjenosti ne poznamo, saj ni enotne definicije teh stranskih učinkov. Drugi stranski učinki so še novo nastala sladkorna bolezen tipa 2, hepatotoksičnost, hemoragična možganska kap in nevrološke motnje. Vsem tem stranskim učinkom navkljub je korist zdravljenja s statini mnogo večja od navedenih stranskih učinkov. Kljub novim terapijam za znižanje holesterola LDL in zato zmanjšani srčnožilni umrljivosti bo terapija s statini še naslednjih nekaj let

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ostala prva izbira tako pri primarni kot tudi sekundarni preventivi, saj še ni dovolj podatkov o dolgoročni učinkovitosti in predvsem varnosti novih zdravil. Nikakor pa ne smemo zanemariti niti ekonomskega vidika, saj je stroškovna učinkovitost statinov v primerjavi z novimi zdravili zaenkrat še mnogo večja.

## 1 Introduction

Statins are one of the most commonly prescribed drugs, reducing cardiovascular morbidity and mortality by lowering LDL cholesterol in both primary and secondary prevention (1). Randomized double-blind studies have shown that lowering LDL cholesterol by 1 mmol/L reduces the relative risk of significant cardiovascular events by 22% (2). Despite the widespread use of statins to lower LDL cholesterol and thus also to reduce cardiovascular morbidity and mortality, discontinuation and non-cooperation are very big problems. The reason for this is most often statin-induced muscle symptoms. Other, significantly fewer common causes are diabetes, neurological and neurocognitive effects, and hepato- and nephrotoxicity (3). The patient's attitude towards the drug depends mainly on their experience and beliefs. Negative beliefs about the drug are an even greater reason for non-cooperation than other factors, such as the price of the drug. A study examining the opinions of statin users on social networks has shown that patients are most often concerned because they do not trust drug manufacturers and because they believe statins are harmful or that they do more harm than good (4). The purpose of this review article is to describe both the positive and negative sides of statin therapy and the possible mechanisms of their action (Figure 1, Table 1).

## 2 Treatment guidelines

In the latest ESC/EAS guidelines for the management of dyslipidaemias from 2019, one of the most important

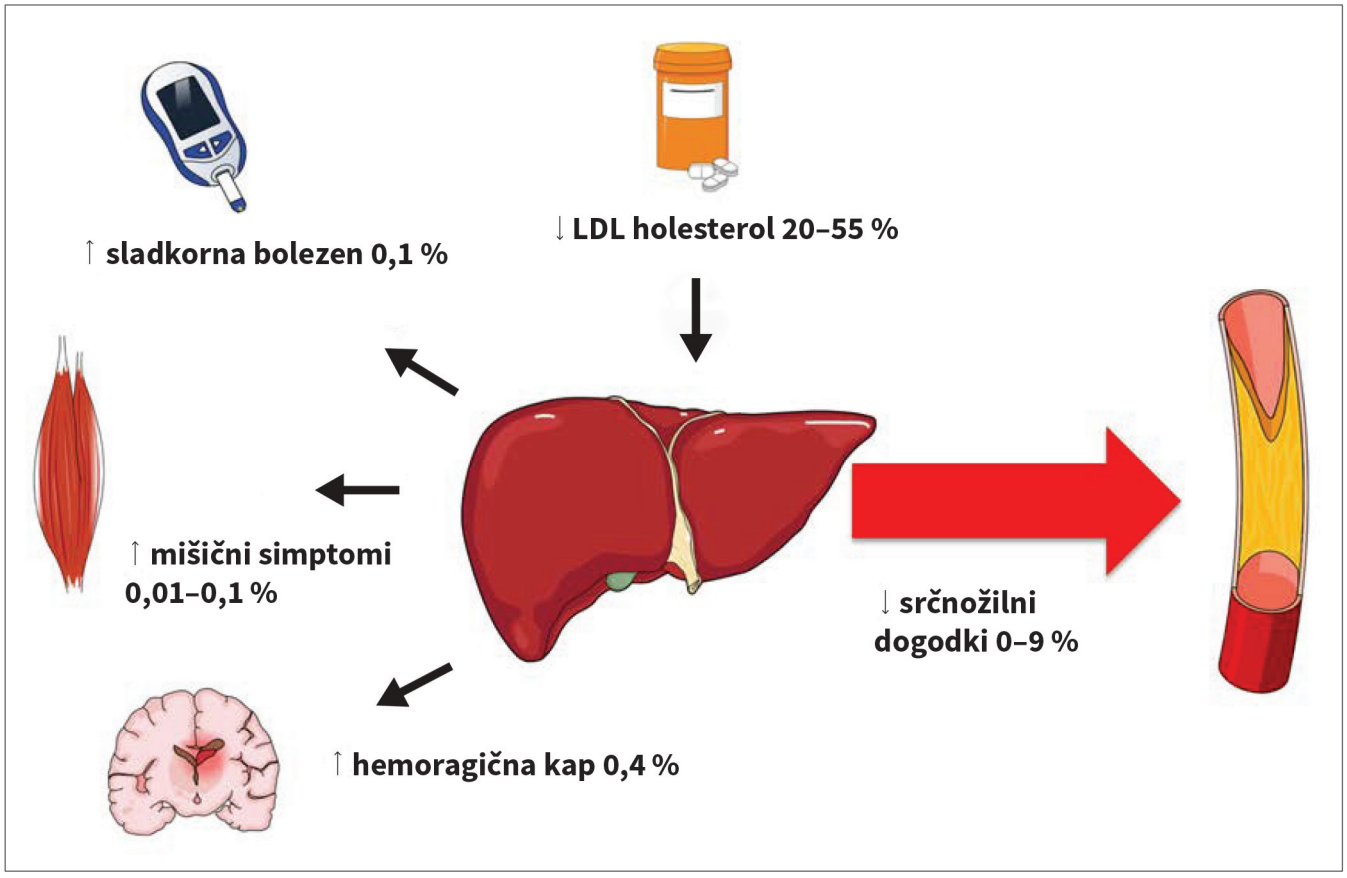


**Figure 1:** Schematic representation of the positive and adverse effects of statins. The numbers shown represent absolute values.

**Table 1:** Positive and adverse effects of statins.

| Positive effects | Adverse effects |
|---|---|
| Statin-induced effects:<br>• reduction of cardiovascular morbidity and mortality;<br>• improvement of endothelial dysfunction;<br>• stabilization of atherosclerotic plaques;<br>• anti-inflammatory effects;<br>• immunomodulatory effects;<br>• antithrombotic effects;<br>• reduction of the risk of dementia;<br>• beneficial effects on bone metabolism. | Statin-induced effects:<br>• myalgia;<br>• toxic myopathy;<br>• immune-mediated myopathy;<br>• rhabdomyolysis.<br>Type 2 diabetes.<br>Neurological and neurocognitive effects:<br>• haemorrhagic stroke;<br>• cognitive decline;<br>• peripheral neuropathy;<br>• depression;<br>• confusion and memory loss;<br>• aggressiveness;<br>• personality changes.<br>Hepatotoxicity.<br>Nephrotoxicity. |

innovations was a change in therapy goals. Target values for lowering LDL cholesterol, which is still the main goal of dyslipidaemia management, are even lower, except in patients at low cardiovascular risk. The recommended reduction in LDL cholesterol level in the group of patients at very high cardiovascular risk is more than 50% or below 1.4 mmol/L, in the high-risk group it is more than 50% or below 1.8 mmol/L, and in the moderate-risk group the target is less than 2.6 mmol/L. Lower LDL cholesterol target values therefore also mean higher treatment intensity. The guidelines state that statin therapy reduces LDL cholesterol by up to 50% and can be used in combination with other cholesterol-lowering drugs. A 1 mmol/L reduction in LDL cholesterol with statins is associated with a 22% reduction in the incidence of significant cardiovascular events, a 23% reduction in coronary events, a 17% reduction in coronary death, a 17% reduction in stroke incidence, and a 10% reduction in all-cause mortality. The beneficial effects are most pronounced in the first year of treatment. The choice of statin depends on the cardiovascular risk and therapy goals of the individual patient, but the response to treatment, associated diseases, and the use of other drugs should always be considered. The guidelines state a strategy for a sequential drug introduction (first high-intensity statin therapy, then ezetimibe, and finally a PCSK9 inhibitor) and mention the possibility of directly adding a PCSK9 inhibitor to statins. If LDL cholesterol target values are not reached at the highest statin dose the patient still tolerates, a combination with ezetimibe is recommended. Combination with a PCSK9 inhibitor is advised in secondary prevention in patients at very high cardiovascular risk who do not reach LDL cholesterol target values at the highest statin and ezetimibe doses. The guidelines also recommend statins as the first drug of choice to reduce cardiovascular risk in patients with hypertriglyceridaemia, but are not effective in some specific patient groups, such as patients with heart failure and those with haemodialysis (5).

The analysis of 19 studies conducted for the US Food and Drug Administration (FDA) included 71,344 patients treated with various statins in primary and secondary prevention over a period of six months to six years. They found that in a group ranging from eight to 286 patients, 72 patients needed to be treated to prevent any cardiovascular event. To prevent one heart attack in groups ranging from 45 to 263 patients, 123 patients had to be treated. One study stated that only 11 patients needed to be treated to prevent one stroke. However, excluding this study, others found that the number of patients needed to be treated to prevent one such event was 263 patients in groups ranging from 92 to 625 patients. All of these studies have shown that diabetes occurred in every 99$^{th}$ subject (6).

## 3 Mechanism of action of statins

The most important effects of statins are lowering LDL cholesterol and thus reducing cardiovascular morbidity and mortality. Statins competitively inhibit the active site of the first and key rate-limiting enzyme of the mevalonate pathway, HMG-CoA reductase. Inhibition of this site prevents access to the substrate, thus inhibiting the conversion of HMG-CoA to mevalonic acid. In the liver, cholesterol synthesis is reduced, which leads to increased production of microsomal HMG-CoA

reductase and increased expression of LDL receptors on the cell surface. This leads to an increased removal of LDL from the bloodstream and thus a 20-55% reduction in LDL levels in it. In addition to lowering LDL levels and reducing cardiovascular morbidity and mortality, statins are thought to have additional pleiotropic effects not related to lipids. These include improving endothelial function, stabilizing atherosclerotic plaques, anti-inflammatory, immunomodulatory and antithrombotic effects, effects on bone metabolism, and reduced risk of dementia. Analysis of some studies has shown that statins reduce the risk of cardiovascular events to a greater extent than just by lowering LDL cholesterol levels, and that they increase survival even in patients who had had a heart attack and who have normal cholesterol levels (7). There are therefore lipid-dependent and lipid-independent mechanisms that contribute to the clinically beneficial effects of statins. Inhibition of HMG-CoA reductase also reduces the production of non-sterol mevalonate derivatives. The most important non-sterol mevalonate derivatives are farnesyl and geranylgeranyl pyrophosphate, which play a key role in protein prenylation and in inhibiting the synthesis of isoprenoid intermediates in the mevalonate pathway (8). Posttranslational protein prenylation, which modifies proteins into more hydrophobic molecules, is important for cell signalling, differentiation, growth regulation, and membrane transport. Non-sterol mevalonate derivatives are thought to be responsible, among others, for the effect of statins on some key reactions in the coagulation and fibrinolysis cascade (9).

The active ingredient of statins is a modified portion of 3,5-dihydroxyglutaric acid, which is structurally similar to the endogenous substrate, HMG-CoA, and the mevaldyl-CoA transition state intermediate. The ring substituents determine the solubility and pharmacological properties of the statin (10,11). Atorvastatin, lovastatin, simvastatin, and fluvastatin are lipophilic and are metabolized by the cytochrome P450 system. Pravastatin and pitavastatin are hydrophilic and due to this property undergo minimal metabolism in the liver. Rosuvastatin is somewhere in the middle in terms of these properties (12).

## 4 Statin toxicity

The most common toxic effects are statin-associated muscle symptoms (SAMS) (13,14). The exact frequency of these side effects is unknown. According to the results of cross-sectional studies, muscle symptoms occur in 10–15% of patients (15-18), and some clinical registries describe as much as 30% incidence of muscle symptoms (14,16). In randomized, double-blind, placebo-controlled studies, the incidence of these symptoms in 1.5–5% of subjects were definitely underestimated, as patients with a history of statin intolerance were excluded from these studies before randomization or during the induction period (14,15,19,20). However, it is also difficult to determine the exact incidence, as there is no single definition for muscle symptoms. Other side effects of statin therapy include the onset of type 2 diabetes, neurological and cognitive effects, hepatotoxicity, impaired renal function, and other less common side effects (21).

Statin toxicity is thought to be a result of inhibition of the HMG-CoA reductase enzyme, direct cellular and subcellular effects, or a combination of both (22). Other possible causes include genetic factors, interactions with other drugs, vitamin D levels, and other metabolic or immune effects (15). Regardless of the mechanism, the end result is a change in the bioavailability and activity of the drug (23). The main predisposing factors are age due to the likely presence of several other diseases (renal or hepatic dysfunction), concomitant use of other drugs that may affect statin function, decreased body weight, and cognitive impairment (17). The only side effects clearly demonstrated in randomized double-blind studies were, in addition to haemorrhagic stroke, muscle symptoms and type 2 diabetes. However, the absolute risk of these side effects is small compared to the absolute benefits of statin therapy (Table 2).

## 5 Statin-associated muscle symptoms

Muscle symptoms are by definition muscle pain, tension or muscle weakness together with an increase in creatinine kinase (CK) concentration to at least ten times the upper limit of normal (24). The most severe form of muscle damage is rhabdomyolysis, which can also lead to acute renal failure or exacerbation of chronic renal failure mainly due to increased concentrations of myoglobin in the blood (25).

Myopathies are rare in patients without associated diseases, although the relative risk of muscle pain is high (25). However, the absolute risk is very small, occurring in one patient per 10,000 patients treated for one year, while the incidence of rhabdomyolysis is two to three patients per 100,000 patients treated for one year (26). From a clinical point of view, muscle symptoms can be divided into four groups: rhabdomyolysis with a high concentration of CK (> 100 times the upper limit of normal (ULN)), myoglobinuria and renal impairment;

**Table 2:** Overview of the most important research on the effect of statins on cardiovascular events and the most common side effects.

| Study (reference) | Subjects (age) | Intervention | Impact on cardiovascular events (ratio of prospects (95% CI)) | Muscle symptoms (% of patients) | Diabetes | Neurological side effects |
|---|---|---|---|---|---|---|
| SEARCH (25) | 12,064 survivors of MI (ages 18–80) | 80 mg simvastatin daily versus 20 mg simvastatin daily | Coronary events (0.94 (0.88–1.01)) stroke (0.85 (0.60–1.21)) | myopathy 53 (1%) versus two (0.03%) | not studied | haemorrhagic stroke (odds ratio (0.91 CI (0.77–1.09)) |
| HPS (26) | 20,536 patients with CHD, PAD or diabetes (ages 40–80) | 40 mg simvastatin daily versus placebo | Coronary events (0.73 (0.76–0.97)) stroke (0.75 (0.66–0.85)) | myalgia 32.9% versus 33.2% | not studied | haemorrhagic stroke 51 (0.5%) versus 53 (0.5%) |
| JUPITER (33) | 17,802 healthy subjects | 20 mg rosuvastatin daily versus placebo | MI (0.46 (0.30–0.70)) stroke (0.52 (0.34–0.97)) total mortality (0.80 (0.67–0.97)) | muscle weakness or pain 1421 (16%) versus 1375 (15.4%) | newly discovered 270 (3%) versus 216 (2.4%) | not studied |
| SPARCL (56) | 4,731 patients who had had a stroke or TIA | 80 mg atorvastatin daily versus placebo | Stroke (0.97 (0.66–0.95)) significant coronary event 81 (3.4%) versus 120 (5.1%) | myalgia 129 (5.5%) versus 141 (6.0%) myopathy 0.3% in both groups | not studied | haemorrhagic stroke 55 (2.3%) versus 33 (1.4%) |
| PROSPER (57,58,59) | 5,804 patients with a history of CD or risk factors (70–82 years) | 40 mg pravastatin daily versus placebo | death due to CHD and MI (0.81 (0.96–0.94)) stroke (0.96 (0.79–1.16)) | myalgia 36 (1.2%) versus 32 (1.1%) | not studied | no differences between the groups |

Legend: CI – confidence interval; HPS – Heart Protection Study; JUPITER – Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin trial; CHD – coronary heart disease; MI – myocardial infarction; PAD – peripheral artery disease; PROSPER – Prospective Study of Pravastatin in the Elderly at Risk; SEARCH – Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SPARCL – Stroke Prevention by Aggressive Reduction in Cholesterol Levels; CD – cardiovascular disease; TIA – transient ischaemic attack.

myalgia or mild increase in CK (< five-fold ULN); self-limiting toxic statin myopathy (CK values between 10 and 100 ULN); myositis or immune-mediated necrotising myopathy with HMG-CoA reductase antibodies and CK values between 10 and 100 times ULN (27).

Regardless of the definition, muscle symptoms usually manifest as symmetrical weakness of large proximal muscles primarily of the lower limbs. Symptoms occur at rest or shortly after physical activity and usually occur within one month after starting treatment or after increasing the dose (15,22). Phenotypically, seven progressively inferior, statin-associated myotoxic phenotypes were proposed. They begin with asymptomatic CK elevation and include tolerable and intolerable myalgia, myopathy, severe myopathy, rhabdomyolysis, and immune-mediated necrotizing myositis (28).

Due to the ability to nonselectively diffuse into the extrahepatic tissues such as skeletal muscle, muscle symptoms are more common in lipophilic statins such as simvastatin, atorvastatin, and lovastatin (15,21). In contrast, hydrophilic statins, which are represented by pravastatin and fluvastatin, have a lower ability to penetrate muscles and therefore a lower risk of muscle symptoms (15). Up to 60% of muscle symptoms are associated with the

concomitant use of statins with drugs metabolized by the same hepatic cytochrome P450 (22). Some believe that the greatest risk for muscle symptoms is previous myopathy with another statin, treatment with high-dose statins, a history of unexplained seizures or elevated CK values in personal history, a family history of muscle symptoms with lipid-lowering therapy, and untreated hypothyroidism (29). Other risk factors include female gender, age over 80, impaired liver or kidney function, alcoholism, consumption of grapefruit juice, vitamin D deficiency, low body mass index, and excessive physical activity.

The SEARCH study (30) reported more than 10 times more myopathies in patients treated with 80 mg simvastatin daily than those treated with 20 mg daily, and the Heart Protection Study (HPS) reported one case per 1,000 or 10,000 patients treated with 40 mg daily for one year (31). Therefore, prescribing the highest doses in all patients is no longer recommended. Regulatory databases also contain a large number of reports of muscle symptoms at high doses of atorvastatin, but these data are very biased and the absolute risk of muscle symptoms even at the highest dose is actually very low (32).

In the HPS study comparing 40 mg simvastatin daily with placebo, there was a relative risk for any form of myalgia of 0.99 (95% confidence interval, 0.95–1.03) regardless of creatinine kinase, while the relative risk of myalgia in patients with creatine kinase levels was more than four times the upper limit of normal, 1.7 (95% confidence interval, 0.9–3.1). In patients whose creatinine kinase levels were increased more than 10-fold above the upper limit of normal, the relative risk was 2.5 (95% confidence interval, 0.8-8.0) (31).

Vitamin D deficiency has been independently associated with muscle weakness and severe myopathy. There is a hypothesis that vitamin D deficiency may exacerbate statin-induced myopathy. In vitamin D deficiency, CYP3A4 is directed to the hydroxylation pathway of vitamin D, which reduces the amount of this metabolite available for statin metabolism, which could increase statin toxicity. Ahmed et al. investigated the association between low vitamin D levels and myalgia in patients receiving statins and the regulation of myalgia with vitamin D replacement while patients continued to receive statins. Patients with vitamin D deficiency were treated with 50,000 units of ergocalciferol per week for 12 weeks. Patients with myalgia receiving statins were found to have lower serum vitamin D levels than patients without myalgia receiving statins. Vitamin D replacement improved muscle symptoms in 92% of patients who were receiving statins and had myalgia and concomitant vitamin D deficiency (33).

Calcium plays a key role in the contraction and relaxation of skeletal muscle, so it is one of the important factors in the formation of SAMS, which includes muscle spasms and cramps. The main pump that allows calcium to be re-absorbed into the sarcoplasmic reticulum is the sarco-endoplasmic reticulum calcium ATPase (SERCA). When SERCA activity was observed in statin users, activity was found to be 30% higher in asymptomatic statin users than in subjects not receiving statin; however, there was no difference between statin users with or without symptoms (34). Increased SERCA activity may impair calcium homeostasis and does not occur as a compensatory mechanism, and its content in skeletal muscle has been shown to decrease after five weeks of endurance training. Therefore, if increased SERCA activity contributes to impaired calcium homeostasis, as shown in statin users, physical activity could benefit such patients (35).

Coenzyme Q10 (CoQ10) is a fat-soluble vitamin-like substance that, when reduced to ubiquinol, protects cells against free radical-induced oxidative stress and is involved in the electron transport in the respiratory chain. Several studies have found that plasma concentrations of coenzyme Q10 are reduced in statin users. Coenzyme Q10 replacement has therefore been suggested for the treatment of SAMS. However, studies have shown that despite the effective increase in serum concentrations of coenzyme Q10, SAMS occurred as often when coenzyme Q10 was replaced as when it was not. Here, too, the occurrence of SAMS has been shown to be multifactorial and unlikely to be related solely to the effect of statins on coenzyme Q10 (36,37).

## 6 Statins and diabetes

The incidence of new-onset type 2 diabetes with statin therapy is higher in patients with pre-existing risk factors such as increased body mass index, higher levels of glycated haemoglobin and impaired glucose tolerance. No differences have been observed between hydrophilic and lipophilic statins, but it appears to be more common in elderly patients and those taking high doses of statins (15). The exact mechanisms by which statins trigger type 2 diabetes are unknown, but there may be direct and indirect effects, including effects on body weight, adipocyte differentiation, blood glucose homeostasis via gluconeogenesis and insulin signalling pathway, changes in concentration and activity of adiponectin and leptin as well as with impaired β-cell function (17,38-40). In understanding the effect of statins on the development of diabetes, it would be helpful to know whether the risk

of developing diabetes during statin therapy is related to the specific action of statins, that is, the inhibition of HMG-CoA reductase, or due to other statin effects.

In 18 studies involving 12,725 patients, they found an average LDL cholesterol reduction of 0.89 mmol/L, while the risk of developing diabetes increased by 10% compared to the control group. These studies included all statins currently on the market, except rosuvastatin. It has been calculated that the risk of developing statin-induced diabetes was 0.1% per year, and that the reduction in cardiovascular events was 0.42% per year (41).

Despite the increased risk of developing diabetes with statin therapy, the benefit of reducing significant coronary events outweighs the potential side effects. In the JUPITER study (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial), which included 17,802 patients without known cardiovascular disease, glycated haemoglobin was slightly higher than placebo after two years of use in the group receiving rosuvastatin (5.9 versus 5.8), which was statistically significant (42,43). There was also a quarter more newly diagnosed diabetes, which was also statistically significant (3.0% vs. 2.4%). Meta-analyses have shown that a standard dose of a statin increases the risk of developing type 2 diabetes by 10%, and higher doses, including rosuvastatin 20 mg used in the JUPITER study, by a further 10% (44,45). Type 2 diabetes usually occurs soon after starting statin therapy, and the risk does not increase with continued treatment. Diabetes usually occurs in patients with already expressed risk factors such as increased body mass index, increased levels of glycated haemoglobin, or impaired glucose tolerance (42,46,47).

A retrospective study of 12,725 patients with type 2 diabetes compared for 3 years the HbA1c levels at six-month intervals between patients who had been treated with statin in the past and patients who did not receive statins but were starting insulin therapy. In the first six months, patients who had received statins in the past had a 0.26% decrease in HbA1c, and the decrease was 0.34% in patients who were not receiving statins. A similar and statistically significant change between HbA1c values was seen even after 12 months. There was a decrease of 0.29% in patients who had received statins in the past and a decrease of 0.37% in patients who were not receiving statins. Patients who had received statins in the past had higher HbA1c levels after three years. A conclusion was made that patients with type 2 diabetes treated with insulin who had received statins in the past experienced a decrease in insulin sensitivity, making insulin treatment less effective in lowering HbA1c (48).

The clinical significance of the increase in the incidence of type 2 diabetes with statin therapy is not entirely clear, as the reduction in cardiovascular morbidity and mortality significantly exceeds the increase in morbidity and mortality associated with diabetes. The incidence of new-onset diabetes in primary prevention is around 1% per year (44), which is around 10–20 new diabetics per 10,000 statin-taking patients per year. If the assumption, that this is associated with a doubling of the risk of cardiovascular disease is made (same as in the case of spontaneous diabetes) (49), then 10,000 patients in primary prevention with a 5 to 10% risk in five years of treatment would have five to ten cardiovascular events. Despite this side effect, lowering LDL cholesterol by 1 to 2 mmol/L in the same patient population prevents 150 to 300 identical events, despite the potentially detrimental effect of new-onset diabetes (50-52).

## 7 Hepatotoxicity

Statin therapy may result in a mild increase in transaminases, which rarely presents a clinically significant hepatic impairment. Elevations in transaminases occur in approximately 3% of patients, usually within the first year of initiation of therapy, and resolve spontaneously despite continued statin use (53-55). Hepatotoxicity is most likely a feature of all statins and is associated with an increase in their dose (56,57).

An increase in transaminases alone, but without an increase in bilirubin, is not unequivocally associated with clinically or pathologically significant hepatocyte damage (58). An even bigger problem is the fact that there is no uniform definition of drug-induced liver injury (DILI).

The exact mechanism of action of DILI is unknown, but in vitro models have shown dose- and time-dependent mitochondrial dysfunction due to statins. In mitochondria, there is thought to be a significant increase in mitochondrial superoxide, which is one of the important cytotoxic and signalling mediators in mitochondrial or hepatic injury. Another important reason for statin-induced hepatotoxicity is that statins cause apoptosis. Cerivastatin was withdrawn from the market in 2001 due to DILI. Other possible mechanisms of hepatotoxicity are inhibition of respiratory chain enzymes, mitochondrial membrane depolarization, and release of calcium ions (59). The incidence of statin-induced liver injury is higher when using statins at maximum doses with other lipid-lowering drugs such as fibrates, other hepatotoxic drugs, or drugs with similar enzyme pathways, or when used in the elderly and people with significant

liver or kidney injury (59). Drug-induced liver injury is relatively rare, with elevated levels of biomarkers of liver injury such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total serum bilirubin, and alkaline phosphatase (ALP) being observed (38). Therefore, active monitoring of liver tests in asymptomatic patients is not recommended in this context. Elevated liver enzymes can be misleading given the actual extent of liver injury. Despite elevated liver enzymes, hepatic adverse reactions are rare. Action is required when symptoms of hepatotoxicity such as fatigue, weakness, loss of appetite, yellowing of the skin or eyes, and dark urine occur (60). A meta-analysis of 135 randomized controlled trials of 246,000 patients receiving atorvastatin, lovastatin, and simvastatin showed that 50% of patients were at increased risk for elevated transaminases compared with placebo. However, there was only a slight increase in values, which did not necessarily mean serious adverse reactions for the liver and usually stabilized over time (61). Statin-induced liver abnormalities have therefore not been demonstrated and are equally common in statin-treated patients and placebo-treated patients. Monitoring of liver enzymes is required when liver dysfunction is present or statins are combined with other hepatotoxic drugs. It is important not to reduce or discontinue statin therapy if liver test values remain below three times the upper limit of normal (62).

## 8 Neurological disorders

The most important and most common neurological disorder is intracerebral haemorrhage. Other neurological disorders for which we have somewhat less data are cognitive decline, peripheral neuropathy, depression, confusion, and memory loss, aggression, and personality changes (21). In observational studies, cholesterol levels were negatively associated with haemorrhagic stroke, especially in patients with elevated arterial blood pressure (63-65). In a randomized, double-blind SPARCL study of 4,731 patients who recovered from cerebrovascular disease, atorvastatin 80 mg statistically significantly reduced ischaemic cerebrovascular events by 21%, but also resulted in a significant increase in haemorrhagic events by 40% (66). When these results are combined with other results from other studies from the CTT meta-analysis (1), the risk of a haemorrhagic cardiovascular event increases by 21% when LDL cholesterol is reduced by 1 mmol/L. However, the reduction in the risk of all cerebrovascular events with statin therapy is greater than the risk of haemorrhagic stroke (52,66). Ribe et al. conducted the largest study to date on the association between statin use and the risk of cerebral haemorrhage in patients who have already had a stroke. More than 55,000 patients were included who started statin therapy after their first intracerebral haemorrhage or ischaemic stroke. They found that the risk of cerebral haemorrhage was similar in patients treated with statins and in those who did not receive statins, regardless of the type of stroke. However, in the subgroup of patients who have previously suffered an ischaemic stroke, the risk is even lower. It was also found that many patients receiving statins start treatment with other drugs after a stroke, which could have a significant effect on the risk of stroke (67).

Regarding the risk of haemorrhagic transformation, a retrospective study was performed comparing patients previously treated with statins, patients who started statin therapy within 3 days after ischaemic stroke, and with patients who were not receiving statins. They found that statin therapy was not associated with early haemorrhagic complications and that statin therapy had not previously affected the treatment of ischaemic stroke with thrombolysis. Early introduction of statins after ischaemic stroke is also not associated with an increased risk of intracerebral haemorrhage (68).

The role of statins in the development of peripheral neuropathy has not yet been clearly demonstrated, and changes in the integrity of cell membranes of neurons, whose important building block is cholesterol, have been described as a possible mechanism. Statins could also affect energy use in neurons by inhibiting coenzyme Q10 (69). According to studies conducted so far, treatment with statins could cause changes in peripheral nerves. But in most cases, these changes do not cause clinically significant symptoms (70).

Cognitive functions during statin therapy were closely monitored in the PROSPER study, which included 5,804 patients aged 72 to 80 years (71-73). Cognitive function was found to be unaffected by treatment with 40 mg pravastatin. Potential memory impairment was closely monitored in the Heart Protection Study (HPS), which followed 20,536 patients taking 40 mg simvastatin daily or placebo for 5 years. It turned out that there were no differences between the groups (31).

It is not entirely clear whether these disorders are caused by the direct action of statins, as the blood-brain barrier selectively permeates so that the brain is self-reliant in endogenous cholesterol synthesis (38). Lipophilic statins are thought to pose a higher risk due to a greater chance of permeating the blood-brain barrier, but these effects are not necessarily specific for statins, but may

be due to low cholesterol (10). Lower serum lipid levels could adversely affect the formation of cell membranes of neurons, myelin sheaths, and nerve synapses. When less cholesterol is available for neurons, this can contribute to a decrease in serotonin activity through decreased receptor expression, which can result in behavioural changes and psychiatric adverse effects (72).

## 9 Other statin-related side effects

Other statin-related side effects include: cataracts, gastrointestinal disorders, urogenital disorders, gynaecomastia, and reproductive disorders. Most are thought to result from reduced formation of intermediates and end products of the mevalonate pathway. Thyroid diseases that are not thought to be statin-related may contribute to statin intolerance, especially in muscle symptoms (17). Meta-analyses have not shown significant effects of statins or lower cholesterol levels using statin on cataract development or prevention. In vitro studies have shown that atorvastatin promotes phagocytosis and reduces inflammation in the retinal pigment epithelium, which may protect against age-related macular degeneration (74). Statins could be associated with lowering androgen as they inhibit the formation of the substrate required for local synthesis. One study found an increased risk of gynaecomastia during statin therapy (75).

## 10 Timing of statin administration

Due to the different half-lives of statins, especially those with a short half-life, the effect is highly dependent on the time of ingestion. Cholesterol biosynthesis changes during the day, peaking between midnight and five o'clock in the morning, so the action of statins during this time can greatly affect the patient's lipid profile. Statins with a short half-life, such as simvastatin, pravastatin, lovastatin, and fluvastatin, should be taken by patients in the evening for best results. Statins with longer half-lives, such as atorvastatin and rosuvastatin are not affected by the timing of administration (76,77). However, there are no data on whether the time of ingestion and concomitant consumption of food affects the occurrence and severity of side effects.

## 11 Drug interactions

Interactions between different drugs occur when previous or concomitant administration of one drug changes the pharmacokinetics or pharmacodynamics of the other drug and therefore the effects of the drugs are different than would be expected from each individual drug. This may lead to a change in the effectiveness or toxicity of one or both drugs. Their effect may be additive, synergistic, or antagonistic, and there may be changes in the absorption, distribution, metabolism, or excretion of the drug. The most clinically important drug interactions are pharmacokinetic and are often due to the induction or inhibition of enzymes and transporters involved in drug metabolism. Most statins undergo microsomal metabolism by the CYP450 isoenzymes and are recognized by transporters in the liver, intestine, and kidney (78). Some genetic variants may contribute to statin toxicity by mutations in genes with the transcription for proteins that regulate pharmacokinetics (receptors, transporters and enzymes) and pharmacodynamics of statins (muscle enzymes) (17). Genetic variants in CYP450 enzyme activity may affect statin interactions with other drugs, while genetic variants in membrane transporters may affect hepatic uptake, circulating concentration, and peripheral tissue exposure (38).

The most common drugs that may interact with statins are glucocorticoids, antipsychotics, HIV protease inhibitors, azoles, immunosuppressants, macrolides, calcium channel blockers, and drugs that affect lipids such as gemfibrozil. Additional reactions can also be caused by alcohol, opioids, and cocaine (22).

## 12 Statins and grapefruit juice

Since the incidental discovery of interactions of grapefruit juice with certain drugs in 1989, interactions with about 85 drugs, including statins, have been identified. The main compounds in grapefruit juice that cause statin interactions are furanocoumarin bergamottin and its derivative 6',7'-dihydroxybergamottin. The compounds inactivate CYP3A4, a key enzyme in the metabolism of some statins. Studies have shown that the concentration of this enzyme in the gastrointestinal tract is reduced by 50% within four hours after drinking grapefruit juice. Inactivation of CYP3A4 in the gastrointestinal tract affects presystemic metabolism of statins and thus increases their systemic availability. This effect occurs only with statins metabolized by CYP3A4, namely lovastatin, simvastatin, and atorvastatin. Fluvastatin, rosuvastatin, and pravastatin are unaffected as they are metabolized by other enzymes. The effect of grapefruit juice on statins drops to 10% of the maximum value 24 hours after drinking it, which means that the half-life of the effect of grapefruit juice is seven to eight hours. For statins with relatively short half-lives, such as simvastatin and lovastatin, drinking grapefruit juice in the

evening when patients also take statin means half the effect of drinking juice in the morning (79).

## 13 »Nocebo« effect

The *placebo* effect is the beneficial effect on health that results from positive expectations during treatment. In contrast, the *nocebo* effect is the detrimental effect on health resulting from negative expectations during treatment. The effects of nocebo and placebo on statin therapy were investigated in three randomized studies: ASCOT, ODYSSEY ALTERNATIVE, and GAUSS-3. The results have demonstrated the effect of nocebo in the placebo groups and have shown that about 20% of patients receiving atorvastatin were in fact intolerant of it (80).

In two large studies, the development of SAMS was observed in patients with statin intolerance. Patients were divided into two groups, one receiving PCSK9 inhibitors and the other ezetimibe. The mechanism of action of both drugs is different from the mechanism of action of statins, so apart from the nocebo effect, no other explanation has been found for the occurrence of this side effect (81,82).

After discontinuation of statin therapy until symptoms have resolved, the time of resuming treatment is crucial for the long-term reduction of the risk of atherosclerotic cardiovascular disease. More than 70% of patients who discontinued treatment due to adverse reactions are expected to reattempt statin therapy. Such patients are offered the option of re-initiating treatment with the same statin dose, possibly at less frequent intervals (e.g. every other day), at a lower dose, or with a different statin. If symptoms persist for more than two months after discontinuing statin therapy, other causes should be assessed (hypothyroidism, rheumatic diseases, etc.) (80).

## 14 Conclusion

The true prevalence of statin intolerance is still not fully understood, but discontinuation of treatment and non-cooperation are a major clinical problem. There are many mechanisms to explain statin toxicity and intolerance, and a major obstacle to detecting these patients is the lack of a clear definition and, above all, a biochemical marker to identify or even predict which patients will develop intolerance or toxicity. However, the vast majority of statin side effects cannot be attributed to just one factor, but to the intertwining of the various mechanisms previously described. Given the relatively high effect on reducing cardiovascular morbidity and mortality and the very low absolute risk of side effects, as well as their cost-effectiveness, statins are likely to be the first drug of choice for the treatment of dyslipidaemia for at least some time. However, further research is needed to find one or more biochemical markers to help us identify patients more likely to have side effects. On the other hand, of course, we need alternative solutions that will enable the treatment of patients with proven adverse effects, which are, nevertheless, rare. Despite the fact that there are drugs that reduce the effect of PCSK9 with antibodies and its synthesis, statins in patients with elevated LDL cholesterol in both primary and secondary prevention are likely to remain the first choice for some time. There is still insufficient data on the long-term efficacy and safety of new drugs.

### Conflict of interest

None declared.

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### List of Abbreviations

ALP = alkaline phosphatase
ALT = alanine aminotransferase
ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial
AST = aspartate aminotransferase
CK = creatine kinase
CTT = Cholesterol Treatment Trialists
CYP3A4 = cytochrome P450 3A4
CYP450 = cytochrome P450
DILI = drug induced liver injury
EAS = European Atherosclerosis Society
ESC = European Society of Cardiology
FDA = Food and Drug Administration
GAUSS-3 = Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3
GGT = gamma-glutamyl transferase
HIV = human immunodeficiency virus
HMG-CoA = hydroxymethylglutaryl-coenzyme A
HPS = Heart Protection Study
IDL = intermediate-density lipoprotein
JUPITER = Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial
LDL = low-density lipoprotein

PCSK-9 = proprotein convertase subtilisin/kexin type 9
PROSPER = Prospective Study of Pravastatin in the Elderly at Risk
SAMS = statin-associated muscle symptoms
SEARCH = Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine
SPARCL = Stroke Prevention by Aggressive Reduction in Cholesterol Levels
ULN = upper limit of normal

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