Statins in clinical medicine

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Summary

Statins inhibit cholesterol biosynthesis. Their main effect is a decrease in circulating levels of LDL cholesterol, which translates into a ~ 20% relative reduction of major vascular events and coronary mortality per mmol/L LDL reduction achieved. Statins are efficient in preventing first cardiovascular events, but the cost-efficiency of primary prevention remains controversial. In primary prevention particularly, the pros and cons of statin therapy should be weighted by considering patient-specific life circumstances and assessing the individual cardiovascular risk, as provided by risk calculators. Since diabetes mellitus poses a high risk even in the absence of known coronary artery disease, statin treatment is generally indicated in these patients. There is no lower LDL threshold defining the limit of treatment benefit; rather, LDL target levels should be sought according to individual cardiovascular risk. If the necessary precautions are taken, e.g., by considering age, co-morbidities and co-medication when choosing the dose, statins are well tolerated and safe, as evidenced by many randomised controlled trials and meta-analyses. If a patient will not tolerate a statin dose necessary to achieve his or her LDL target level, ezetimibe may be added. There is no indication that statins alter cancer risk. Despite recent evidence that statin treatment is associated with a small risk of incident diabetes mellitus, this disadvantage is outweighed by the vascular benefits. Statins have pleiotropic effects, such as anti-inflammatory properties. It is still debated to what extent these effects translate into cardiovascular risk reduction beyond that conferred by LDL reduction.

Key words: statins; HMG-CoA reductase inihibitors; cholesterol LDL; safety cancer diabetes

Introduction

Statins rank among the most frequently prescribed drugs in today's clinical practice. These substances are either fungal-derived analogs (lovastatin, pravastatin, simvastatin) of the originally isolated agent, mevastatin [1], or fully synthetic compounds (fluvastatin, cerivastatin, atorvastatin, rosuvastatin, pitavastatin). Statins competitively inhibit the rate-limiting enzyme of cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, thereby reducing intracellular cholesterol levels

(fig. 1; [2]). This causes upregulation of low-density lipoprotein (LDL) receptors and thus reduction of circulating LDL cholesterol levels. In 1994, the "4S" study was the first megatrial investigating the benefits of statin treatment over placebo in a high-risk Scandinavian population [3]. In patients with established coronary artery disease (CAD), simvastatin treatment in "4S" not only significantly reduced cardiovascular morbidity, but also overall and coronary mortality by 30 and ~ 40%, respectively. Later statin trials demonstrated a significant reduction in cardiovascular events also in patients without known CAD [4–6], even if baseline LDL concentrations were low, i.e., at a level comparable to or even lower than those achieved by simvastatin treatment in "4S" [7, 8]. Besides their main effect of lowering atherogenic LDL-cholesterol levels, statins have a number of pleiotropic effects [9], which may contribute to the vascular benefits; however, to which extent pleiotropic statin effects translate into a clinically meaningful benefit remains a matter of debate.

Cardiovascular risk reduction achieved by statin treatment: implications from randomised controlled trials and meta-analyses

Efficacy and safety of statins

Since the report of the "4S" study [3], a large number of randomised controlled trials have demonstrated the beneficial effects of statins on major vascular events and mortality rates over a wide range of clinical settings and patient groups [10]. A meta-analysis performed by the Cholesterol Treatment Trialists' (CTT) collaborators, including individual patient data from 90,000 participants in 14 randomised controlled statin trials, 11 of which used a placebo-control, demonstrated a relative reduction of ~ 20% in major vascular events (nonfatal myocardial infarction or coronary death, coronary revascularization, and ischemic stroke) per mmol/L reduction in LDL levels [11]. Coronary and overall mortality were also shown to decrease by ~ 20% and 12%, respectively, per mmol/L LDL reduction. Importantly, there was no apparent risk for first incident cancers or non-vascular deaths (see below, section on side-effects and safety profile).

Another large meta-analysis included 76 randomised controlled trials with 6 different statins and a total of 170,000

participants [12]. Only studies using an inert control design were analysed. The authors found that all major vascular events, including the composite outcome of fatal and non-fatal stroke, as well as all-cause mortality, were significantly reduced by statin treatment. The analysis found no indication for an increased risk of hemorrhagic strokes associated with statin use, a concern which had been raised previously [13]. Statin treatment was not associated with an increased incidence of cancer, elevation of creatin kinase, or rhabdomyolysis. However, elevation of liver enzymes occurred significantly more often, and a significantly higher rate of new incident diabetes mellitus was observed (see below, section on side-effects and safety profile). The authors could not demonstrate differences in therapeutic effects between the statins used in the trials.

The very large body of data integrated in these two meta-analyses exemplifies the efficiency and safety of statin treatment in many clinical settings and over a wide age range. There are, however, some important safety issues to consider when prescribing statins, particularly regarding potential drug interactions. These are discussed in a separate paragraph below.
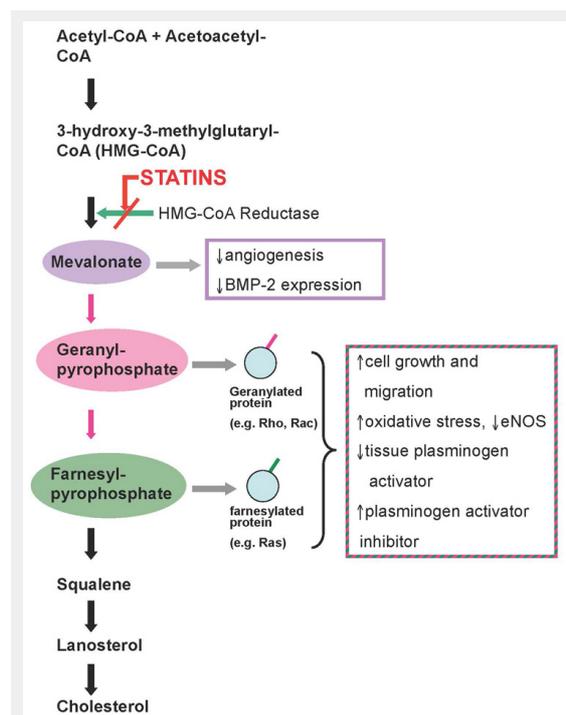
Statins in patients with diabetes mellitus

A subgroup analysis by the CTT collaborators investigated the statin effects in nearly 19,000 patients with diabetes mellitus, mostly type 2, which comprised ~ 20% of the total number of the CTT collaborators' study subjects [14]. The reductions in all-cause mortality and major vascular events observed in diabetics were comparable to those in non-diabetics and were demonstrated irrespective of the patients' history of vascular disease. The CTT collaborators' findings established that in patients with diabetes mellitus, but no history of vascular disease, the 10-year risk for a major vascular event exceeds 20%, thus warranting much the same LDL target levels and intervention strategies as in high-risk non-diabetics, i.e., patients with known vascular disease. Consequently, the American Diabetes Association (ADA) recommends LDL levels of <2.6 mmol/L as target for diabetics without overt cardiovascular disease (CVD); LDL <1.8 mmol/L is an option in those with established CVD. Specifically, the ADA recommends statin therapy in all diabetics with known CVD regardless of age and baseline lipid levels, as well as in those without known CVD but over 40 years old and with one or more other CVD risk factors [15]. In lower risk situation, such as primary prevention or age <40 years, statins are recommended if LDL is >2.6 mmol/L. In clinical practice, the ADA standards implicate that most patients with type 2 diabetes mellitus should be treated with a statin, although there are no specific guidelines as to treatment indications in connection with long-term metabolic control, or the time point when treatment should start after a diagnosis of type 1 diabetes.

Statins in patients with chronic kidney disease

Patients with chronic renal failure are at a very high cardiovascular risk, but several randomised controlled statin trials had failed to show vascular benefits in patients who had received renal transplants [16], as well as patients undergoing chronic hemodialysis [17, 18]. The recently published SHARP trial investigated the effect of simvastatin/ezetimibe versus placebo in over 9,000 patients with chronic kidney disease, 3,000 of which were on maintenance dialysis [19]. In SHARP, after a mean follow-up of 4.9 years, there was a significant relative risk reduction of 17% for the combined primary outcome of a first atherosclerotic event (non-fatal myocardial infarction, coronary death, non-hemorrhagic stroke, and arterial revascularisation) in the simvastatin/ezetimibe group [20]. Importantly, there were no differences between patients undergoing dialysis and those in earlier stages of chronic kidney disease. The differences in outcome between SHARP and earlier statin trials in renal failure are remarkable [21]. They may be explained by the SHARP trial's large size and higher statistical power, as well as by its specific focus on atherosclerotic events.

Lipid target levels

How low should LDL target levels be in a given clinical situation, and is there a lower LDL threshold indicating the limit of treatment benefit or even a risk for untoward statin effects? Unlike suggested by earlier studies [22], later trials, such as the Heart Protection Study [6], the PROVE IT–TIMI 22 trial [23] or the TNT study [24] demonstrated that the proportional cardiovascular risk reduction per mmol/L LDL reduction is maintained even when achieved LDL levels are below 2 mmol/L. Accordingly, the revised

Figure 1

Essential steps of cholesterol biosynthesis. Pink arrows indicate that several intermediate molecules are not depicted.
Statins inhibit the rate-limiting step of cholesterol synthesis, which is catalysed by HMG-CoA reductase.
Pleiotropic statin effects are mediated by mevalonate and prenylated signaling molecules (Rho, Rac, Ras), as indicated in colored boxes.
BMP-2, bone morphogenetic protein-2. e-NOS, endothelial nitric oxide synthase.
Adapted, with permission, from Rutishauser J, Schweiz Med Forum. 2008;8(10):187–90, www.medicalforum.ch.

Adult Treatment Panel III (ATP III) guidelines of the National Cholesterol Education Program (which will be succeeded by the ATP IV guidelines in 2012) state LDL cholesterol levels of <1.8 mmol/L as a therapeutic option in very high risk patients [25]. Recently, the SEARCH trial investigated, in 12,000 high-risk patients, the efficacy and safety of intensive LDL lowering with 80 mg compared to 20 mg simvastatin daily over a mean follow-up of 6.7 years [26]. The greater LDL reduction by 0.35 mmol/L in the intensely treated group was accompanied by a relative risk reduction of 6% for major vascular events, confirming the magnitude of proportional risk reduction calculated by the CTT collaborators. Death rates were not different in the two groups; in particular, there were no differences in non-vascular deaths, which had been an adverse trend in the TNT study [24].

The CTT collaborators also assessed the efficacy and safety of intensive LDL lowering in a meta-analysis of individual data from 170,000 patients [27], adding 12 more studies to their original analysis published in 2005. 5 studies (comprising ~ 40,000 patients) compared higher versus lower statin dosage, the remainder had a controlled design using placebo or, rarely, usual care in the control group. As compared to less intensive treatment, higher statin doses further reduced major vascular events in similar proportions, per mmol/L LDL reductions, as in placebo-controlled trials. The proportional reductions of coronary death or non-fatal myocardial infarction, coronary revascularisations, and ischemic strokes persisted when the data of all 26 studies, including those with achieved LDL <2 mmol/L, were combined [27].

Patients with heart failure

Recently published randomised controlled statin trials have specifically focused on patients with congestive heart failure. In the CORONA trial, which included 5,000 elderly patients with ischemic systolic heart failure and a mean ejection fraction of 31%, rosuvastatin treatment over 36 months, as compared to placebo, reduced LDL-cholesterol and high-sensitivity C-reactive protein (CRP) concentrations, but did not significantly reduce the composite primary outcome of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [28]. The reason for this negative finding is unclear. Similarly, the GISSI-HF trial evaluated rosuvastatin versus placebo over a mean follow-up of 3.9 years in 4,600 patients with heart failure; this study also included patients with non-ischemic heart failure or with preserved ejection fraction, i.e. diastolic failure [29]. Co-primary endpoints were time to death and time to death or hospital admission for cardiovascular disease. Despite effective lowering of LDL cholesterol levels, these outcomes were not reduced by rosuvastatin as compared to placebo treatment. Thus, although earlier concerns about potentially hazardous effects of statins in patients with heart failure were not confirmed by the CORONA and GISSI-HF trials, they both failed to demonstrate efficacy on clinically relevant outcome measures. The authors of the GISSI-HF trial concluded from their data that it is reasonable not to start statins in patients with non-ischemic heart failure, perhaps even to stop them. Given the favourable trend for the primary endpoint in the CORONA trial and the positive safety profile documented in both CORONA and GISSI-HF, it seems warranted to prescribe statins for the individual patient with heart failure according to his or her estimated risk for cardiovascular events.

Treatment initiation after a cardiovascular event

A clinically relevant question addresses the timing of statin therapy after a cardiovascular event with respect to short-term benefits. It has become common clinical practice to start previously untreated patients who present with acute coronary syndrome on statins immediately. But how good is the evidence base for this? The PROVE IT–TIMI 2 trial compared moderate and intensive LDL reduction with pravastatin and atorvastatin, respectively, in patients hospitalised with an acute coronary syndrome [23]. Patients were randomised a median of 7 days after the cardiac event. Death or a subsequent major vascular event occurred significantly less often when LDL reduction was more aggressive, and this benefit, which lasted over the follow-up period of 30 months, became detectable as early as 30 days. Similarly, the MIRACL study investigated the benefit of early (within 24 to 96 hours) initiation of atorvastatin treatment versus placebo in patients with unstable angina or non-Q-wave infarction [30]. During the follow-up of 16 weeks, atorvastatin-treated patients experienced significantly less recurrent ischemic cardiac events. These and other trials [31] have probably contributed to today's common use of immediate statin therapy in patients hospitalised with acute coronary disease. However, while this therapeutic "reflex" compromised patient recruitment in a large trial designed to evaluate the benefit of early statin treatment after acute coronary events [32], it is not sufficiently backed by data. In fact, several studies were unable to demonstrate an early benefit of statin treatment on recurrent vascular events after acute coronary syndrome [32–34]. A meta-analysis on short-term vascular outcomes [35], which was recently updated to include 18 randomised controlled trials and 14,000 patients [36, 37], could not demonstrate a benefit of early statin treatment on the composite outcome of death, non-fatal myocardial infarction, and non-fatal stroke 1 and 4 months after the index event, even though the analysis considered only studies with an inert control and excluded those comparing two differing statin regimens (e.g., PROVE IT–TIMI 22 [23]). In light of these data, it seems difficult to maintain that early statin therapy after acute (cardio) vascular events has clinically relevant short-term benefits which would warrant or even necessitate immediate initiation of treatment.

Interestingly, in the setting of non-cardiac vascular surgery, a beneficial short-term statin effect has been documented in one randomised controlled trial (DECREASE III study [38]). Perioperative treatment with fluvastatin reduced the relative risk of postoperative myocardial ischemia by 45% as compared to placebo (absolute risk reduction, 8.2%; number needed to treat for 30 days, 12). This effect was paralleled not only by a reduction of LDL levels, but also of various markers of inflammation. It remains uncertain to which extent pleiotropic effects (e.g., plaque stabilisation) may have contributed to the favourable study result.

Statins for the primary prevention of vascular disease

Randomised controlled trials have unequivocally demonstrated the efficacy of statins to prevent first cardiovascular events in persons without known CAD, with LDL cholesterol levels considered high [39], moderately elevated [4], or average [5, 7] at the time of recruitment. Several large intervention trials have included persons with and without known CAD. E.g., in the Heart Protection Study, roughly one third of the 20,000 participants had no history of coronary disease [6]; prevention of a first major vascular event by simvastatin treatment was equally efficient in these individuals as in those with prior myocardial infarction or other coronary heart disease. As suggested by the PROSPER trial, in which 55% of the 5,800 participants had no history of coronary heart disease, primary CAD prevention with statins may be less efficient in elderly persons [40]. As for primary stroke prevention, a meta-analysis of 65 trials with 200,000 participants showed comparable statin effects for patients with (relative risk reduction: 25%) or without (relative risk reduction: 23%) coronary heart disease [41]. However, the numbers needed to treat in order to prevent a first stroke were considerably higher than to prevent a cardiovascular event.

The JUPITER trial assessed whether treatment with rosuvastatin would reduce first major cardiovascular events in patients without CAD or hyperlipidemia (LDL-cholesterol levels <3.36 mmol/L), but considered at high vascular risk due to elevated (≥2 mg/L) high-sensitivity CRP levels [42]. 17800 participants were randomised. After a median follow-up of 1.9 years, the trial was stopped early following an interim efficacy analysis showing a relative risk reduction of 44% for rosuvastatin [8]. The number needed to treat (nnt) for 2 years to prevent one primary end point was 95, the projected nnt for 5 years would be 25. The treatment benefit was maintained in all analyzed subgroups, including patients with a low (<10%) Framingham risk score, and was largest in the individuals who achieved both low LDL (<1.8 mmol/L) and low high-sensitivity CRP (<1 mg/L) levels [43]. The authors of the JUPITER trial emphasised the potential of anti-inflammatory drug effects in the treatment of vascular disease; however, the hypothesis that inflammation status, as evidenced by elevated baseline CRP levels, modifies the beneficial effects of statin treatment has been challenged on the basis of data from the Heart Protection Study [44].

So how can clinicians substantiate their treatment decisions in primary prevention of vascular disease, particularly CAD? Costs are a major factor in today's health care systems, but whether statin treatment in primary prevention is cost-effective is still a matter of debate [45, 46]. Before starting drug therapy, all modifiable cardiovascular risk factors should be addressed. Treatment benefits and potential harms (e.g., slightly increased diabetes risk; see below) should be considered and discussed with the patient. Available current guidelines, such as the National Institute for Health and Clinical Excellence (NICE) guideline 67 [47], recommend statins are drugs of choice for primary prevention in individuals with high cardiovascular risk (i.e., ≥20% over 10 years) as assessed with a recommended risk score.

In Switzerland, the risk engine provided the *Arbeitsgruppe Lipide und Atherosklerose* (AGLA; www.agla.ch), uses an algorithm based on data from the PROCAM study to stratify patients according to their individual 10-year cardiovascular risk. Target LDL values appropriate for the calculated risk are offered. Thus, a probabilistic approach should be the basis for the decision for or against pharmacological treatment in primary prevention of vascular disease, and individual patient settings should be taken into account, rather than lipid levels only.

Use of ezetimibe in clinical medicine

Ezetimibe inhibits dietary and biliary cholesterol absorption into enterocytes, resulting in a ~ 14–20% incremental LDL reduction compared to treatment with statin alone [48, 49]. Favourable statin effects on HDL cholesterol and triglyceride levels are also augmented by ezetimibe. The substance is marketed as single compound or combination tablet with simvastatin. Simvastatin/ezetimibe was used in a recent study investigating the effect of lipid-lowering therapy in patients with asymptomatic, mild to moderate aortic stenosis (SEAS trial, [50]). After a mean follow-up of 4.35 years, the combined primary outcome of ischemic and aortic valve events did not differ between the groups receiving simvastatin/ezetimibe or placebo, nor did the secondary outcomes of aortic valve replacement or clinical progression of aortic valve stenosis. There was a significant excess of incident cancers in the simvastatin/ezetimibe group, which did not occur at any particular site (see below, section on side-effects and safety profile).

Another mega-trial with simvastatin/ezetimibe (IMPROVE-IT) compares the benefits of adding ezetimibe to simvastatin monotherapy in 18,000 patients after acute coronary syndromes [51]. The study has completed inclusion, and follow-up is expected to end in mid-2013 (www.clinicaltrials.gov; trial registration number NCT00202878). As of now, the SHARP trial thus remains the only positive outcome study with simvastatin/ezetimibe (see above, section on chronic kidney disease).

According to current guidelines, ezetimibe is recommended as treatment option in hypercholesterolemia, either as monotherapy if statins are contraindicated or not tolerated, or as an adjunct, e.g., if the statin dose needed to reach the individual target level is not tolerated (e.g., www.nice.org.uk: NICE technology appraisal guidance 132, issued Nov. 2007, reviewed Aug. 2010; www.agla.ch). Of note, however, ezetimibe as monotherapy has never been shown to have clinically relevant anti-atherogenic potential.

Non-LDL (pleiotropic) effects of statin treatment: limited clinical data

By inhibiting HMG-CoA reductase, statins reduce intracellular levels of isoprenylated signaling molecules, thereby inhibiting inflammatory and oxidative reactions in endothelial cells, reducing platelet adhesion and proliferation of vascular smooth muscle cells, and influencing other processes involved in atherogenesis (fig. 1; [9]). The contribution of pleiotropic statin effects to improved cardiovascular

outcome is a matter of ongoing debate [52]. In most clinical trials reporting on pleiotropic effects of statins, these were not the primary outcome measures, or they were evaluated in a retrospective manner. E.g., a recent case-control study found a significant reduction of gallstones associated with statin use, possibly due to decreased cholesterol concentration in bile [53]. According to systematic reviews and meta-analyses, statins may also be beneficial in the treatment and prevention of infections [54], reduce short-term mortality after an episode of pneumonia [55], and lower morbidity and mortality in COPD patients [56]. However, randomised controlled outcome trials specifically addressing the hypotheses generated by observational data are often missing. The systemic anti-inflammatory effects of statins, as evidenced by reduction of high-sensitivity CRP levels, were prospectively demonstrated, amongst others, in the JUPITER trial [8]. Interestingly, atorvastatin significantly reduced the incidence of venous thromboembolism, but the absolute risk reduction during 1.9 years of mean follow-up was only 0.3% [57]. Data suggesting a reduction of the risk of atrial fibrillation by statins have not been confirmed by a recent meta-analysis [58]. Thus, the contribution of non-LDL – mediated statin effects to clinical outcomes is still debated, and randomised clinical trials addressing non-cardiovascular statin benefits remain scarce [59, 60].

Side effects and safety profile of statins

Drug interacations
Although statins have been proven to be generally well tolerated, specific issues on safety and side-effects may arise in clinical practice. It is particularly important to be aware of potential interactions with other frequently prescribed medications, which may increase the risk of untoward effects. Simvastatin and fluvastatin, unlike pravastatin and rosuvastatin, show significant metabolism by cytochrome P (CYP) 450 enzymes. Thus, co-substrates or inhibitors of CYP 3A4 or CYP 2C9 may increase circulating levels of simvastatin and atorvastatin, or fluvastatin, respectively. But even if CYP 450 metabolism is only weak, as in pravastatin, statin concentrations may rise significantly in patients with renal failure taking CYP 450 substrates or inhibitors. Also, co-administration of antagonists to hepatic organic anion-transporting polypeptides (OATP), or of inhibitiors of glucuronidation, may cause

statin toxicity irrespective of CYP 450 metabolism. Table 1 summarizes important information about drug interactions of statins with other frequently prescribed drugs.

Myopathy
Myalgia may occur in as much as 7% of patients taking statins [61]. The risk for statin-induced myopathy, i.e., clinical symptoms and elevation of creatin kinase, increases with higher statin dose and the presence of co-factors, such as age, renal failure, or co-medication interfering with the cytochrome P metabolism of the statin in question (for details, see [52]). A genome-wide search conducted in 85 participants of the SEARCH trial [26] who had developed myopathy on the high dose (80 mg daily) simvastatin treatment identified common genetic variants in the gene encoding the organic anion-transporting polypeptide 1B1. Variants were associated with increased risk for simvastatin-induced myopathy [62]. This finding was replicated also in the Heart Protection Study. Since the transporter protein mediates hepatic uptake of several statins (as well as other drugs), it is likely that the results from SEARCH and the Heart Protection Study are applicable to statins other than simvastatin.

Cancer risk
Controversial data have been published on statins and cancer risk. A case-control study suggested that the use of statins is associated with a 47% reduction in relative risk for colorectal cancer [63]. Conversely, the CARE trial had reported an increased incidence of breast cancer associated with pravastatin use [22], and in PROSPER, which studied pravastatin treatment versus placebo in the elderly, cancer incidence rose in the pravastatin arm [40]. In the SEAS trial, incident cancers were significantly more frequent in the simvastatin/ezetimibe than in the placebo arm [50], but when the data were combined with the SHARP and IMPROVE-IT trials, both ongoing at the time of the analysis, there was no evidence of an adverse effect of ezetimibe on cancer risk [64]. The interpretation of data on cancer incidence in statin trials is problematic, since it may take longer than the follow-up periods (i.e., ~ 3 to 5 years) for cancers to develop *de novo*. A 10-year follow-up of the 4S study found no difference in cancer mortality and cancer incidence between the original simvastatin and placebo groups [65]. The efficacy and safety analysis by the CTT collaborators studied site-specific cancer incidents, considering trials comparing high versus low statin doses, statin treatment versus placebo, and all trials combined. There

Table 1: Compounds interacting with statin metabolism. Frequently administered drugs that may increase statin levels and toxicity by different mechanisms. The list is not exhaustive.

Inhibitors/substrates of Cytochrome P 450 enzymes involved in statin metabolism	Inhibitors of hepatic organic anion transporter transporter protein (OATP)	Inhibitor of glucuronidation
Clarithromycin Amiodarone Verapamil Diltiazem Antifungal agents (azoles) Grapefruit juice Coumarines Cyclosporine A Sulfonylureas HIV antiretrovirals	Gemfibrozil Cyclosporine A HIV antiretrovirals	Gemfibrozil

was no risk of increased cancer incidence at all sites or at any particular site, nor was there a detectable risk of increased cancer mortality associated with statin use, as evidenced by rate ratios per mmol/L LDL reduction [27]. In accordance with most of the studies mentioned above, a large meta-analysis showed a neutral effect of statins on cancer incidence and cancer death [66]. Thus, current data do not support the notion that statin therapy alters cancer risk.

Diabetes mellitus

The CORONA study reported a small, non-significant increase in newly diagnosed diabetes in the rosuvastatin as compared to the placebo group [28]. In the JUPITER trial, the median HbA1c values were minimally, but significantly higher in the rosuvastatin than the placebo group (5.9% versus 5.8%, respectively), and the incidence of physician-reported diabetes was significantly higher in the rosuvastatin arm [8]. Two recent meta-analyses investigated the relation between statin use and development of diabetes. Sattar et al. identified 13 major randomised controlled cardiovascular outcome trials, each with over 1,000 participants and a follow-up period of more than one year [67]. In 7 of these trials, data on diabetes incidence had not been previously reported. Although the absolute event rate varied considerably between studies, statin therapy was associated with a significant increase in new diabetes (odds ratio, 1.09). Risk appeared higher with increasing age. Mills et al., in their meta-analysis of 76 randomised controlled trials, analysed data on incident diabetes available from 17 studies enrolling 111,000 individuals [12]. They calculated a significant, 9% relative increase in diabetes risk associated with statin treatment, confirming the findings of Sattar et al. Based on these data, it can be concluded that statin therapy carries a small, but significant risk of developing diabetes. While this risk is outweighed by the proven cardiovascular benefit, it should be taken into consideration when statin treatment is evaluated in persons at lower cardiovascular risk [67].

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References

1 Endo A. The discovery and development of HMG-CoA reductase inhibitors. J Lipid Res. 1992;33(11):1569–82.

2 Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundamental and Clinical Pharmacology. 2005;19(1):117–25.

3 Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344(8934):1383–9.

4 Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333(20):1301–7.

5 Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998;279(20):1615–22.

6 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360(9326):7–22.

7 Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003;361(9364):1149–58.

8 Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195–207.

9 Zhou Q, Liao JK. Pleiotropic effects of statins. – Basic research and clinical perspectives. Circulation Journal. 2010;74(5):818–26.

10 Lardizabal JA, Deedwania P. Lipid-lowering therapy with statins for the primary and secondary prevention of cardiovascular disease. Cardiol Clin. 2011;29(1):87–103.

11 Cholesterol Treatment Trialists' (CTT) Collaborators. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267–78.

12 Mills EJ, Wu P, Chong G, Ghement I, Singh S, Akl EA, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. QJM. 2011;104(2):109–24.

13 Amarenco P, Bogousslavsky J, Callahan A, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355(6):549–59.

14 Cholesterol Treatment Trialists' (CTT) Collaborators. Kearney PM, Blackwell L, Collins R, Keech A, Simes J, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371(9607):117–25.

15 Executive summary: Standards of medical care in diabetes – 2010. Diabetes Care. 2010;33(Suppl 1):S4–10.

16 Holdaas H, Fellström B, Jardine AG, Holme I, Nyberg G, Fauchald P, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. Lancet. 2003;361(9374):2024–31.

17 Wanner C, Krane V, März W, Olschewski M, Mann JFE, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353(3):238–48.

18 Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360(14):1395–407.

19 SHARP Collaborative Group. Study of Heart and Renal Protection (SHARP): Randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. Am Heart J. 2010;160(5):785–94.e10.

20 Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181–92.

21 Stevens KK, Jardine AG. SHARP: a stab in the right direction in chronic kidney disease. Lancet. 2011;377(9784):2153–4.

22 Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996;335(14):1001–9.

23 Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350(15):1495–504.

24 LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart J-C, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352(14):1425–35.

25 Grundy SM, Cleeman JI, Merz CNB, Brewer HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. In: Circulation. 2004:227–39.

26 SEARCH Collaborative Group. Armitage J, Bowman L, Wallendszus K, Bulbulia R, Rahimi K, et al. 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(9753):1658–69.

27 Cholesterol Treatment Trialists' (CTT) Collaboration. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. 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(9753):1670–81.

28 Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JGF, Cornel JH, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med. 2007;357(22):2248–61.

29 GISSI-HF Investigators. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008;372(9645):1231–9.

30 Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA. 2001;285(13):1711–8.

31 Sato H, Kinjo K, Ito H, Hirayama A, Nanto S, Fukunami M, et al. Effect of early use of low-dose pravastatin on major adverse cardiac events in patients with acute myocardial infarction: the OACIS-LIPID Study. Circulation Journal. 2008;72(1):17–22.

32 Thompson PL, Meredith I, Amerena J, Campbell TJ, Sloman JG, Harris PJ, et al. Effect of pravastatin compared with placebo initiated within 24 hours of onset of acute myocardial infarction or unstable angina: the Pravastatin in Acute Coronary Treatment (PACT) trial. Am Heart J. 2004;148(1):e2.

33 Liem A, van Boven AJ, M VNIG, Withagen AJ, Robles de Medina RM, Tijssen JGP, et al. Effect of fluvastatin on ischaemia following acute myocardial infarction: a randomized trial. Eur Heart J. 2002;23(24):1931–7.

34 de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KAA, White HD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004;292(11):1307–16.

35 Briel M, Schwartz GG, Thompson PL, de Lemos JA, Blazing MA, van Es G-A, et al. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. JAMA. 2006;295(17):2046–56.

36 Briel M, Vale N, Schwartz GG, de Lemos JA, Colivicchi F, den Hartog FR, et al. Updated evidence on early statin therapy for acute coronary syndromes: Meta-analysis of 18 randomized trials involving over 14000 patients. Int J Cardiol. 2011; epub ahead of print.

37 Vale N, Nordmann AJ, Schwartz GG, de Lemos J, Colivicchi F, den Hartog F, et al. Statins for acute coronary syndrome. Cochrane database of systematic reviews (Online) 2011;6CD006870.

38 Schouten O, Boersma E, Hoeks SE, Benner R, van Urk H, van Sambeek MRHM, et al. Fluvastatin and perioperative events in patients undergoing vascular surgery. N Engl J Med. 2009;361(10):980–9.

39 Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006;368(9542):1155–63.

40 Shepherd J, Blauw GJ, Murphy MB, Bollen ELEM, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360(9346):1623–30.

41 Briel M, Studer M, Glass TR, Bucher HC. Effects of statins on stroke prevention in patients with and without coronary heart disease: a meta-analysis of randomized controlled trials. Am J Med. 2004;117(8):596–606.

42 Ridker PM, JUPITER Study Group. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. Circulation. 2003;108(19):2292–7.

43 Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Kastelein JJ, et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet. 2009;373(9670):1175–82.

44 Heart Protection Study Collaborative Group. C-reactive protein concentration and the vascular benefits of statin therapy: an analysis of 20536 patients in the Heart Protection Study. Lancet. 2011;377(9764):469–76.

45 Greving JP, Visseren FLJ, de Wit GA, Algra A. Statin treatment for primary prevention of vascular disease: whom to treat? Cost-effectiveness analysis. BMJ. 2011;342d1672.

46 Taylor F, Ward K, Moore TH, Burke M, Davey Smith G, Casas J-P, et al. Statins for the primary prevention of cardiovascular disease. Cochrane database of systematic reviews (Online) 2011(1):CD004816.

47 Cooper A, Nherera L, Calvert N, O'Flynn N, Turnbull N, Robson J, et al. Clinical Guidelines and evidence review for lipid modification: cardiovascular risk assessment and the primary and secondary prevention of cardiovascular disease. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners 2008.

48 Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. JAC. 2002;40(12):2125–34.

49 Gagné C, Bays HE, Weiss SR, Mata P, Quinto K, Melino M, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol. 2002;90(10):1084–91.

50 Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med. 2008;359(13):1343–56.

51 Cannon CP, Giugliano RP, Blazing MA, Harrington RA, Peterson JL, Sisk CM, et al. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. Am Heart J. 2008;156(5):826–32.

52 Rutishauser J. The role of statins in clinical medicine – LDL – cholesterol lowering and beyond. Swiss Med Wkly. 2006;136(3-4):41–9.

53 Bodmer M, Brauchli YB, Krähenbühl S, Jick SS, Meier CR. Statin use and risk of gallstone disease followed by cholecystectomy. JAMA. 2009;302(18):2001–7.

54 Tleyjeh IM, Kashour T, Hakim FA, Zimmerman VA, Erwin PJ, Sutton AJ, et al. Statins for the prevention and treatment of infections: a systematic review and meta-analysis. Arch Int Med. 2009;169(18):1658–67.

55 Douglas I, Evans S, Smeeth L. Effect of statin treatment on short term mortality after pneumonia episode: cohort study. BMJ. 2011;342d1642.

56 Dobler CC, Wong KK, Marks GB. Associations between statins and COPD: a systematic review. BMC Pulmonary Medicine. 2009;932.

57 Glynn RJ, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. N Engl J Med. 2009;360(18):1851–61.

58 Rahimi K, Emberson J, Mcgale P, Majoni W, Merhi A, Asselbergs FW, et al. Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials. BMJ. 2011;342d1250.

59 McCarey DW, McInnes IB, Madhok R, Hampson R, Scherbakov O, Ford I, et al. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. Lancet. 2004;363(9426):2015–21.

60 Lee T-M, Lin M-S, Chang N-C. Usefulness of C-reactive protein and interleukin-6 as predictors of outcomes in patients with chronic ob-

structive pulmonary disease receiving pravastatin. Am J Cardiol. 2008;101(4):530–5.

61 Oskarsson B. Myopathy: five new things. Neurology. 2011;76(7 Suppl 2):S14–9.

62 SEARCH Collaborative Group. Link E, Parish S, Armitage J, Bowman L, Heath S, et al. SLCO1B1 variants and statin-induced myopathy – a genomewide study. N Engl J Med. 2008;359(8):789–99.

63 Poynter JN, Gruber SB, Higgins PDR, Almog R, Bonner JD, Rennert HS, et al. Statins and the risk of colorectal cancer. N Engl J Med. 2005;352(21):2184–92.

64 Peto R, Emberson J, Landray M, Baigent C, Collins R, Clare R, et al. Analyses of cancer data from three ezetimibe trials. N Engl J Med. 2008;359(13):1357–66.

65 Strandberg TE, Pyörälä K, Cook TJ, Wilhelmsen L, Faergeman O, Thorgeirsson G, et al. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). Lancet. 2004;364(9436):771–7.

66 Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. JAMA. 2006;295(1):74–80.

67 Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010;375(9716):735–42.
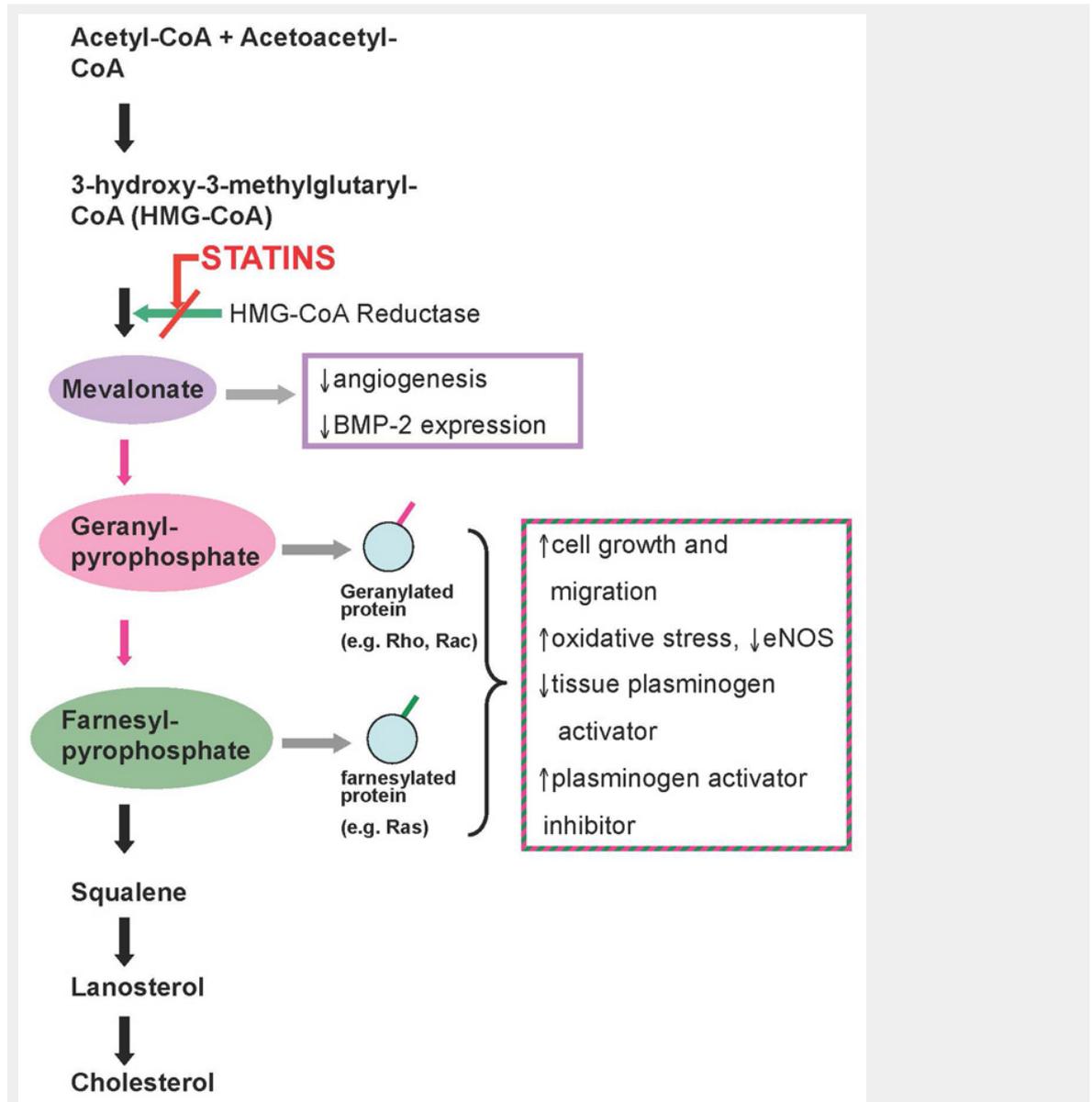
Figures (large format)

Figure 1

Essential steps of cholesterol biosynthesis. Pink arrows indicate that several intermediate molecules are not depicted. Statins inhibit the rate-limiting step of cholesterol synthesis, which is catalysed by HMG-CoA reductase.

Pleiotropic statin effects are mediated by mevalonate and prenylated signaling molecules (Rho, Rac, Ras), as indicated in colored boxes.

BMP-2, bone morphogenetic protein-2. e-NOS, endothelial nitric oxide synthase.

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