

The role of statins in clinical medicine – LDL – cholesterol lowering and beyond

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Summary

In the past years, statins have emerged as the most important class of lipid lowering agents. Through inhibition of HMG-CoA reductase, they restrict the rate-limiting step of cholesterol synthesis, which leads to upregulation of LDL receptors on the cell membrane and thus reduction of atherogenic LDLs. This effect translates into clinical benefit by reducing cardiovascular events both in primary and secondary prevention settings. As an approximate rule, statin therapy leads to a relative risk reduction of 25–30% in most of the large randomised controlled trials. Stroke risk is reduced to a similar degree. Despite initial concerns, the currently available statins have a favourable safety profile; however, potential interactions with

other drugs must be considered. Recently, characteristics unrelated to LDL lowering have been intensively studied. These pleiotropic statin effects result from decreased levels of isoprenoid intermediates of cholesterol synthesis. They include – among others – anti-inflammatory, anti-proliferative, and immunomodulatory actions. Pleiotropic effects favourably influence pathomechanisms of plaque formation. Furthermore, they may prove beneficial in the prevention or treatment of diseases unrelated to atherosclerosis, eg rheumatoid arthritis, multiple sclerosis, or cancer.

Key words: statins; HMG-CoA reductase inhibitors; cholesterol; LDL; effects, pleiotropic

Introduction

The identification of hypercholesterolaemia as a key cardiovascular risk factor fuelled intensive research for compounds that would inhibit the rate-limiting enzyme in cholesterol synthesis, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. In 1971, Japanese chemists initiated a project which led to the isolation of the first statin, mevastatin, from 600 litres of *penicillium citrinum* culture filtrate [1]. The compound lowered serum cholesterol in hens, dogs and primates, including humans, and led to the development of other HMG-CoA reductase inhibitors [2]. Lovastatin, simvastatin, and pravastatin were approved and marketed by 1990, and since then, fluvastatin, atorvastatin, cerivastatin, and rosuvastatin have followed. Interestingly, during the early days of the statin era the safety of cholesterol lowering therapy in general was questioned [3]. The WHO trial, a primary prevention study with clofibrate in hyperlipidaemic patients, had reported a signifi-

cant elevation of non-cardiac deaths during the treatment phase which levelled off after treatment was terminated [4]. The Lipid Research Clinics study with cholestyramine [5] and the Helsinki heart study with gemfibrozil [6] also found an elevated non-coronary death rate, compared with placebo, particularly due to accidents and violence, but the increases were not significant. Nevertheless, as late as 1992 the British Medical Journal asked: “Should there be a moratorium on the use of cholesterol lowering drugs?” [7]. But at that time, the statins had already begun their triumphant success, and since the early 1990s, tens of thousands of individuals have been allocated to statin treatment in many randomised controlled trials. According to an internet source (www.newstarget.com/003425.html), 126 million subscriptions have been filled for statins in 2004, 30% more than in 2003. These figures underscore the socioeconomic significance of these drugs.

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Cardiovascular risk reduction

The foremost effect of all statins is the lowering of blood atherogenic LDL levels. LDL reduction by the available statins may range from ~20% to maximally ~55%; elevation of HDL levels is clearly less pronounced with 0% to ~10% reported [8, 9]. Several early as well as recent studies reported reduction of progression or even regression of coronary lesions as measured by angiography [10–14]. Similarly, in venous coronary bypass grafts, lowering of LDL-cholesterol with lovastatin slowed the progression of graft atherosclerosis as measured by angiography [15]. The “4S” study with simvastatin, published in 1994, was the first placebo-controlled megatrial to demonstrate a reduction of cardiac mortality and morbidity as well as overall mortality in a high-risk population with established coronary artery disease (CAD) and an elevated mean LDL cholesterol level of 4.87 mM [16]. Other large trials followed. The CARE trial was a secondary intervention study in patients after myocardial infarction with mean

LDL-cholesterol levels of 3.59 mM [17]. Treatment with pravastatin led to a relative risk reduction for coronary events of 24% compared to placebo. The LIPID study with pravastatin showed similar relative risk reductions for cardiovascular events in a secondary prevention setting with patients after myocardial infarction or unstable angina [18, 19]. Furthermore, LIPID also documented a significant reduction in overall mortality [18]. The same is true for HPS (Heart Protection Study), a large trial evaluating simvastatin versus placebo in over 20 500 very high-risk patients with or without known CAD and mean pre-treatment LDL-levels of 4.3 mM [20]. The PROSPER trial looked at an elderly population aged 70–82 years, about 45% of which had a history of vascular disease [21]. In these patients, lowering LDL-cholesterol by approximately one third over three years reduced cardiac events by 19%; overall mortality was unchanged.

Primary prevention studies

A large body of clinical data suggests that the benefit of statin treatment is not limited to patients with known CAD. In the West of Scotland Coronary Prevention Study (WOSCOPS) none of the nearly 6600 high-risk males with elevated LDL levels (mean, 4.96 mM) had a history of myocardial infarction, and only 5% reported angina. In these individuals, pravastatin reduced the relative risk for coronary events (including cardiac death) by ~30%, and for overall mortality by 22% as compared to placebo [22]. Even more astonishing, the AFCAPS/TexCAPS trial demonstrated that lovastatin reduces the relative cardiac risk to a similar degree also in individuals with average LDL cholesterol levels (mean, 3.89 mM) and without a pronounced coronary risk profile [23]. In the HPS, 35% of patients reported no prior CAD, and only ~45% of the participants in PROSPER had a history of coronary, cerebral, or peripheral vascular

disease. Recently, the ASCOT-LLA trial looked at over 10000 hypertensive patients with ≥ 3 additional cardiovascular risk factors, but without known CAD [24]. These individuals had mean LDL-cholesterol levels as low as 3.4 mM. Nonetheless, atorvastatin treatment resulted in a relative reduction of major cardiovascular events by 36%. In the CARDS trial, which studied nearly 3000 type 2 diabetics without CAD, treatment with atorvastatin resulted in an equal relative risk reduction for major cardiovascular events [25]. However, although statins in the setting of primary prevention effectively reduce cardiovascular events, the economic consequences of this therapy must be kept in mind. Thus, it was concluded from a cost-effectiveness analysis that statin treatment in primary prevention should be limited to high-risk individuals [26].

Specific patient groups, clinical settings and outcomes

Diabetes mellitus

Subgroup analyses in the large secondary prevention trials have been of limited meaning, because the number of included patients with diabetes mellitus was low (~1590 of a total of >17 600 subjects studied in 4S, CARE, and LIPID). Nevertheless and not surprisingly, the data from these studies suggested a similar cardiovascular benefit for diabetics as for non-diabetics (eg [27] for the CARE trial). In the primary prevention trials, WOSCOPS and

AFCAPS/TexCAPS, a total of 13200 persons were studied, of which ~300 diabetics. This was not enough to draw a conclusion about the benefit of statin treatment in diabetic patients in the primary prevention setting. Similarly, the ASCOT-LLA primary prevention study was underpowered and/or had too short a follow-up (median, 3.3 years) to prove a benefit for diabetics [24]. These issues were clarified by the HPS. 5963 diabetics were included, 3982 of which without CAD and 2912 without any

known arterial disease. These patients benefited significantly from treatment with simvastatin with regard to coronary and cerebrovascular events and revascularisations (relative risk reduction for any major vascular event, 22%) over a wide range of specified variables such as age, duration and type of diabetes, HbA_{1c} level, presence or absence of hypertension, waist circumference, and creatinine levels [28]. The risk reduction occurred irrespective of the pre-treatment LDL-levels. The CARDS study [25] exclusively studied diabetic patients, in which the baseline mean LDL concentration was somewhat lower than in the HPS study population (3 vs 3.4 mM, respectively). CARDS corroborated the findings of HPS. Treatment with atorvastatin reduced the risk of a first major cardiovascular event by 37%. Thus, these data warrant statin treatment of diabetic patients even in a setting of primary prevention. Although direct evidence exists for simvastatin and atorvastatin only, there is no reason to believe that other statins will not yield a comparable benefit. Should all type 2 diabetics be treated with statins? This question is under debate [29] and may well be negated. Multiple factors such as age, comorbidity, and socio-economic situation must be taken into account when making a treatment decision. The UKPDS risk engine represents a helpful tool to predict CHD and stroke risk in type 2 diabetes and may thus facilitate treatment decisions (<http://www.dtu.ox.ac.uk/index.html?maindoc=/riskengine>).

Acute coronary syndrome and percutaneous coronary interventions

In 3000 patients with unstable angina or non-Q-wave acute myocardial infarction, the MIRACL study demonstrated a 16% relative risk reduction by treatment with high-dose atorvastatin, compared to placebo, for a composite cardiac endpoint during 16 weeks after randomisation [30]. The LIPS trial looked at statin-mediated benefits in >1600 patients with coronary catheter interventions [31]. Fluvastatin significantly reduced the risk for a major cardiac event during 4 years of follow-up. A subgroup analysis of the PRISM trial in acute cardiac ischaemia also confirmed the benefit of statins in the acute ischaemic episode by demonstrating that discontinuation of statin therapy in pre-treated patients is related to an increased risk of recurrent events during the follow-up of 30 days [32]. Recently, the PROVE-IT trial compared high-dose (80 mg) atorvastatin versus standard-dose (40 mg) pravastatin therapy in 4162 patients with acute coronary syndrome [33]. Although designed as a non-inferiority trial, the study found a benefit of the aggressive therapy regarding a composite endpoint including death from any cause and stroke. The findings of PROVE-IT will be further discussed below in the section on the pleiotropic statin effects.

Effect on stroke risk

The causal relationship between dyslipidaemia and stroke risk is less clearly documented than that

between hypercholesterolaemia and CAD. Thus, a meta-analysis of 45 studies with 450000 patients failed to demonstrate a relationship between total cholesterol levels and stroke rate, except in patients <45 years old [34]. However, most of the cited studies reported fatal strokes only, and the distinction between ischaemic and haemorrhagic stroke was not made. The 4S study showed no benefit on stroke mortality, which was a component of the composite primary endpoint. However, in a post-hoc analysis, the relative risk for fatal and non-fatal stroke was 70% in those patients allocated to simvastatin [16]. Subgroup analyses of the LIPID and CARE trials demonstrated a relative risk reduction of 19% and 31%, respectively [17, 18]. In the primary prevention setting of WOSCOPS, the relative risk reduction was only 11%, and the low absolute risk resulted in a very high number needed to treat (642 to avoid 1 stroke event for the mean follow-up period of 4.9 years; >3000 per year). The overall beneficial effect in all three pravastatin studies resulted entirely from a reduction in non-haemorrhagic strokes [35]. Thus, the more studies became available, the more evident was the benefit of statin treatment on stroke risk [36, 37]. However, so far, no data exist on statin benefits in the secondary prevention of stroke in patients without known CAD. PROSPER, although focused on a high-risk elderly population surprisingly showed no reduction on stroke rate [21]. This finding may be explained by the low stroke incidence observed in the study population and the relatively short follow-up of 3.2 years. In the HPS, the relative reduction in ischaemic strokes (28%) paralleled that in major coronary events [20, 38]. Based on the meta-analyses of the large statin trials, the authors calculated a 21% risk reduction for every 1 mM reduction in LDL levels. CARDS even reported a 48% risk reduction for strokes in diabetics, higher than that for acute coronary events [25]. Taken together, most of the available clinical data clearly support a beneficial effect of statins on ischaemic stroke risk, in a range comparable to that on coronary events.

Chronic kidney disease

So far, one trial has studied the effect of atorvastatin on cardiovascular events in ~1200 type 2 diabetics undergoing chronic haemodialysis, a population with very high cardiovascular risk [101]. Surprisingly, despite a marked drop in LDL cholesterol of 42% in the atorvastatin group, no reduction was found in the composite primary cardiovascular endpoint as compared with placebo over a follow-up of four years. Overall and CHD mortality did not change either. In marked contrast to the studies mentioned above, there was even a two-fold risk for fatal strokes in the atorvastatin- compared to placebo-treated patients. The lack of therapeutic benefit in this study may result from differing pathogenetic mechanisms of cardiovascular disease in patients on haemodialysis, but the negative findings remain essentially unexplained.

Pleiotropic effects of statins

Whether the favourable effect on the serum LDL concentration is the sole explanation for the clinical benefit of the HMG-CoA reductase inhibitors is an interesting and intensively studied question. Although acute lowering of LDL concentrations by a single apheresis improves endothelial-dependent vasodilation as assessed by forearm blood flow measurement [40], several lines of evidence suggest that statins have features that cannot be explained by lowering of the LDL levels alone. These cholesterol-independent, so-called pleiotropic effects [41] on non-hepatic tissues have been observed with various statins, even the hydrophilic pravastatin, which penetrates poorly through cell membranes of non-hepatic cells. It has therefore been hypothesised that pleiotropic statin effects could in part be mediated by a reduction in circulating levels of hepatic cholesterol precursors [42].

In the absence of a clear-cut causal relation between LDL elevation and stroke risk, the statin benefit on stroke incidence may be viewed as indirect evidence for pleiotropic effects. These may concern either neuronal cells or, in the case of the hydrophilic pravastatin, which in therapeutic concentrations does not pass the blood-brain barrier, endothelial cells (see below). Another clue for pleiotropic effects comes from the 10-year report of the POSCH trial [43], which studied the effect of partial ileal bypass surgery on cardiac events. POSCH demonstrated a 37% reduction, compared to the non-operated control group, of coronary morbidity and mortality along with changes in lipid profiles similar to those achieved by statin therapy. However, while in many statin trials the effects were fully discernible after three years of treatment, leading to premature termination of the studies in some instances, the event curves in the POSCH study started to separate only at ~3 years and continued to do so until approximately 10 years of follow-up. The relatively early benefit of the statin treatment could thus result from additional pleiotropic effects.

Plaque stabilization and endothelial homeostasis

The MIRACLE trial demonstrated that aggressively dosed statin therapy significantly reduced recurrent coronary events within 16 weeks in patients with acute coronary syndrome [30]. In the PROVE-IT study, the advantage of the high over the standard statin dose led to a separation of the event curves as early as three weeks after the initiation of treatment. Moreover, the reduction of the hazard ratio became significant already after 180 days [33]. How could such rapid effects be explained? Via inhibition of HMG-CoA reductase, statins lower concentrations of intermediate products of cholesterol synthesis, the isoprenoids. Post-translational modification through isoprenylation of GTP-binding proteins, such as Rho, Ras or Rac,

is crucial for the correct function and localisation of these molecules. They are involved in the regulation of the cell cycle, endothelial nitric oxide synthase expression, smooth muscle cell migration, tissue plasminogen activator (tPA) / tPA inhibitor expression, NAD(P)H oxidase activity, and other cellular functions relevant in the proliferative and oxidative processes of plaque formation [42]. In plaques obtained and analysed from humans *ex vivo*, pravastatin treatment has been shown to increase collagen content and reduce metalloproteinase activity, thereby counteracting factors that lead to plaque destabilisation and rupture [44]. In a mouse model of focal cerebral ischemia, simvastatin and lovastatin reduced infarct size via up-regulation of endothelial NO synthase [45], which, among other effects, promotes vasodilation and inhibits platelet aggregation. Thus, the impact of statins on atherosclerotic lesions exceeds their effect on plaque size by mere reduction of lipid contents.

Anti-inflammatory and immunomodulatory effects

The CRP level has been identified as independent predictor for future cardiovascular events [46–48]. The post-hoc analysis of the CARE trial demonstrated that pravastatin treatment led to a decrease of CRP levels, which rose continuously in the placebo-treated group [49]. The lowering of CRP was independent of the effect on LDL levels. This finding was confirmed in the prospective PRINCE study with pravastatin [50]. Moreover, in the AFCAPS/TexCAPS study, lovastatin reduced the CRP level significantly, and there were more first coronary events in patients with CRP levels higher than median even when LDL levels were low [51]. In the PROVE-IT study, the achieved CRP levels predicted the cardiac outcome irrespective of the achieved LDL levels [52]. A post-hoc analysis of the REVERSAL trial, which had demonstrated a reduced coronary atheroma progression with 80 mg atorvastatin compared to 40 mg pravastatin [14], reported that the decrease in CRP levels was correlated independently with atheroma progression. The atheroma size regressed in the patients with the greatest reductions in CRP levels, but not in those with the greatest LDL reductions [53]. These hypothesis-generating studies suggest that the anti-inflammatory action of statins, whatever mechanism responsible, could translate into a clinical benefit irrespective of that achieved by lowering the LDL levels. It should be kept in mind, however, that CRP levels in patients with CAD fluctuate substantially [54]. This may hamper the use of CRP as a parameter for risk stratification and treatment monitoring. So far, there have been no studies using CRP levels as primary target to guide statin treatment. The JUPITER trial will include up to 15 000 subjects with low (<3.36 mM) LDL and elevated (>2 mg/L)

high-sensitive CRP levels to test the effect of rosuvastatin on cardiovascular events in a primary prevention setting [55].

Immunomodulatory effects of various statins have been investigated *in vitro* and *in vivo*. Interferon γ -induced expression of major histocompatibility complex II molecules on human endothelial and macrophages is inhibited specifically and in a dose-dependent manner by atorvastatin, lovastatin, and pravastatin [56]; thus, statins may be regarded as potentially immunosuppressive. Indeed, in an earlier study in patients with cardiac transplants, those treated with pravastatin not only had less graft vasculopathy and intimal thickness, but also less severe rejections than those receiving placebo [57]. However, none of the large statin trials has reported an increased risk of serious infections, which could be expected if statins were potent immunosuppressors. Although fluvastatin was shown to lower cardiac event rates in kidney transplant recipients [58], it failed to reduce the rate of allograft rejection in a randomised, placebo-controlled trial [59].

Interesting clinical observations were made in patients with autoimmune diseases. Two open-label pilot studies using simvastatin and lovastatin reported regression of gadolinium-enhancing lesions in patients with relapsing-remitting multiple sclerosis [60, 61]; however, clinical disability scores were unchanged. In contrast, in a randomised, placebo-controlled trial in patients with rheumatoid arthritis, the TARA study, atorvastatin, given in combination with standard disease-modifying drugs, not only lowered markers of inflammation but had a modest, but significant effect on clinically defined disease activity [62].

Effects on bone and fracture risk

Through interference with isoprenylation of GTP-binding proteins, lovastatin has an inhibitory effect on osteoclasts *in vitro* [63]. Additionally, a stimulating effect on bone formation in mice has been demonstrated for simvastatin, lovastatin, mevastatin, and fluvastatin; simvastatin increases expression levels of bone-morphogenetic protein-2 via action on its gene promoter [64]. Statins may thus have a therapeutic potential in osteoporosis prevention and/or treatment [65]. In observational studies, statin use was associated with a decreased fracture risk in postmenopausal women [66] as well as mixed populations [39, 67]. In these studies, the adjusted odds ratios for statin users were as low as ~50%. On the other hand, an analysis using the same data base as in ref. [67] found no beneficial effect of statin use on fracture risk [68], and a post-hoc analysis of the LIPID trial

found equal fracture rates in the pravastatin- and placebo-treated group [69]. Thus, the benefit of statins on fracture risk remains uncertain, and controlled trial designed for this endpoint are lacking.

Effects on risk for dementia

Observational studies have suggested significant reductions in the risk for various forms of dementia [70, 71] as well as for Alzheimer's disease [72]. However, these results may be influenced by indication and cessation bias and have been subject to debate [73]. A placebo-controlled randomised study with simvastatin over 6 months in 35–70 year-old adults even found adverse effects on neuropsychological tests [74]. In the PROSPER and HPS studies, no differences on cognitive function were seen between the treatment groups [20, 21]. Effects on cognition were, however, not part of the primary and secondary endpoints.

Statins and cancer

By reducing the intracellular isoprenoid pool, lovastatin has been shown in cell culture experiments with various tumour cells to induce apoptosis, initiate cell cycle arrest, induce differentiation, and regulate various signalling pathways involved in tumour growth (reviewed in [75]). Cerivastatin inhibits proliferation and invasiveness of cultured breast cancer cells [76]. On the other hand, in the CARE study, the incidence of female breast cancer rose in the pravastatin group, and the PROSPER trial reported a significantly higher number of new cancer diagnoses in the pravastatin compared to the placebo group [21], with the highest hazard ratios for breast and gastrointestinal tumours (1.65 and 1.46, respectively). A meta-analysis of the cancer incidence in the major pravastatin trials, however, was performed in the PROSPER report which failed to detect an elevated cancer risk. A 10-year follow-up of the 4S study found no differences in mortality and cancer incidence in the original simvastatin and placebo groups [77]. Recent case-control studies even found slight decreases in breast cancer risk in postmenopausal women [78] and a 20% relative risk reduction for various cancers in a mixed population [79]. In a population from northern Israel, the use of statins for ≥ 5 years was associated with a 47% relative risk reduction for colorectal cancer [80]. However, due to the low incidence and hence absolute risk, the number needed to treat to prevent one case is >4800 . Taken together, the epidemiological data – in the absence of prospective endpoint studies – suggest that statin use is safe or may even have a protective effect on cancer incidence.

Target LDL levels: how low is low enough?

The question of how intensely LDL cholesterol should be lowered has been addressed from both a socioeconomic and a biological point of view [81, 82]. While an earlier post-hoc subgroup analysis of the CARE trial suggested that no further benefit resulted if LDL levels were lowered to <3.21 mM [83], recent trials clearly draw a different picture. The HPS in particular demonstrated that a distinct LDL-threshold cannot be defined, as the relative risk reduction of ~25% was preserved even in participants whose LDL was lowered to <2 mM [20]. In PROVE-IT, cardiovascular benefit was achieved by lowering LDL to 1.6

mM. Moreover, TNT, which compared two doses of atorvastatin, achieved 2 mM in the high dose (80 mg) group, for a relative risk reduction of 22% of total major cardiovascular events. Notably, in TNT, overall mortality did not differ between treatment groups [84]. In the light of recent clinical data, the executive summary on the detection, evaluation, and treatment of high blood cholesterol in adults (ATP III), which dates from 2001 [85], has been amended with a recent guideline [86]. LDL goals are defined according to the cardiovascular risk category. For high risk patients (10 year risk estimated >20%), LDL <1.8 mM is given as “optional goal”, with <2.6 mM remaining the standard. For practical purposes, scores to calculate an individual patient’s risk category are available (eg, the PROCAM scheme [87]).

Thus, the therapeutic goals have become more ambitious, particularly for high-risk patients. Nevertheless, the indication and goals of statin therapy must be evaluated critically. Although the log-linear relationship between LDL-levels and cardiovascular risk predicts an equal relative risk reduction irrespective of the baseline LDL level [81, 86], the absolute risk reduction abates with decreasing baseline LDL (see figure). Consequently, the number needed to treat increases. Thus, as the motivation to initiate statin treatment rises, so do the costs, and the advantages and disadvantages of statin therapy must therefore be weighed for every patient individually.

Figure 1

The absolute cardiac risk reduction by statin treatment is shown as a function of mean baseline LDL levels in various clinical trials. Primary prevention studies are presented in italics

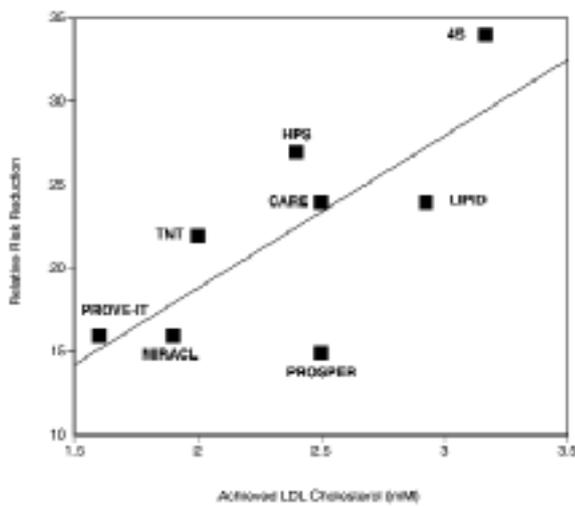


Table 1

Pharmacological properties of statins.

	Lovastatin	Simvastatin	Pravastatin	Fluvastatin	Atorvastatin	Rosuvastatin
CYP Metabolism	3A4	3A4	not significant	2C9	3A4	2C9
Lipophilia	yes	yes	no	yes	yes	no
Approx. elimination half life (h)	2	3	3	3	14	19
Approx. equivalence dose* (mg)	40	20	40	>40	10	<10

* for LDL reduction; cf. refs. [8, 9]

Adverse events and drug interactions

Statin toxicity is in part idiosyncratic, but clearly shows dose-dependency as well. Myopathy may manifest as myalgia only but may also present as severe rhabdomyolysis. Elevation of kreatine kinase (>10× upper limit of normal) was very rare in the large statin trials and occurred to a similar degree under placebo (eg, 30 cases under statin treatment, 29 under placebo in >30000 participants of the CARE, LIPID, WOSCOPS, 4S, and AFCAPS/TexCAPS trials [88]). The pathogenesis of statin-induced myositis is unclear (mitochondrial toxicity? Selenoprotein deficiency [89]?). Elevation of liver transaminases to >3× upper limit of normal occurred in the percent range and not more often in the statin- than in the placebo-

treated groups in the large trials. The TNT study, however, demonstrated the dose dependency of this adverse event, which occurred in 0.2% of patients treated with 10 mg atorvastatin and 1.2% of those treated with 80 mg [84]. Similar observations were made in the PROVE-IT trial [33]. Recently, the safety of rosuvastatin, the most potent HMG-CoA reductase inhibitor currently available, has been debated for higher risk rates of renal toxicity and rhabdomyolysis than other statins [90, 91]. Case-reports [92] and a case-control study [93] have described axonal peripheral neuropathy under statin use, and thrombotic thrombocytopenic purpura has been observed as well [94, 95].

When suspecting statin-associated adverse

events, it is important to consider a patient's comorbidity and comedication. Since statins are eliminated partly by the kidney, doses need to be adapted in patients with severe renal insufficiency. Special attention should be paid to pharmacological interactions [96]. With the exception of pravastatin, statins are metabolised by the cytochrome P 450 (CYP 450) enzymes (table 1). Inhibitors of CYP 3A4 include macrolide antibiotics, azoles, protease inhibitors, verapamil, diltiazem, amiodarone, warfarin and grapefruit juice. CYP 2C8/9 is inhibited by gemfibrozil, phenytoine, losartan, diclofenac, ibuprofen, and tolbutamide. These agents potentially augment statin toxicity. Gemfibrozil and cyclosporine A inhibit the hepatic statin transporter, OATP-C, thereby potentially increasing their bioavailability [97]. Gemfibrozil also inhibits glucuronidation of statin metabolites [98]. The case of cerivastatin highlights the importance of pharmacological aspects in statin toxicity. It has a high intrinsic activity and a high bioavail-

ability (~60%, compared to ~5-20% in other statins). Many of the patients who developed fatal rhabdomyolysis were treated simultaneously with gemfibrozil. The combination of these factors led to 52 deaths among cerivastatin-treated patients and consequently the withdrawal from the market in 2001. Simvastatin and atorvastatin are substrates of P-glycoprotein, a transport protein involved in biliary and renal excretion of drugs and drug metabolites. Therefore, simvastatin and atorvastatin may increase plasma concentration of other P-glycoprotein substrates, such as digoxin [99].

Overall, statins proved to have a favourable safety profile both according to data reported in large trials and in post-marketing surveillance. The initial fears of increased non-cardiac death rates have been abolished, and if individual factors such as age, hepatic and renal function, and comedication are given adequate thought, treatment is safe for patients in a wide age range.

Conclusion and outlook

Statins have become the mainstay of cholesterol lowering treatment. Their benefit on cardiovascular event rates, including ischaemic stroke, has been demonstrated in many large-scale randomised controlled trials. On the other hand, limitations of statin effects have also become evident, eg they do not influence the progression of calcific aortic stenosis [100], and a recent atorvastatin study with diabetics receiving haemodialysis failed to show a benefit on a composite CAD and stroke endpoint [101].

In summary, although statins do not represent

the miracle cure for all vascular problems, they have great clinical potential, and their fascinating pleiotropic effects may open the field for novel therapeutic indications in the future.

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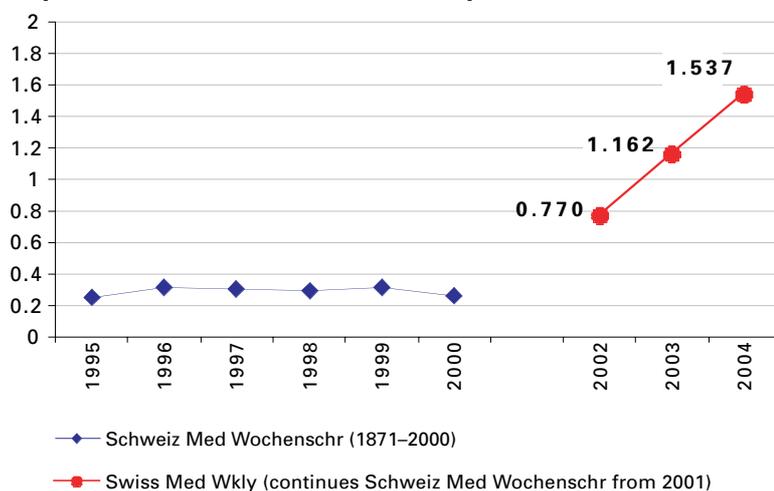
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