Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Invited article: Current opinion | Published 3 February 2012, doi:10.4414/smw.2012.13515
Cite this as: Swiss Med Wkly. 2012;142:w13515

Statins: have we found the Holy Grail?

Raban Jeger, Thomas Dieterle

Cardiology, University Hospital, Basel, Switzerland

Summary

In coronary artery disease, cardiovascular risk factors are the main targets for primary and secondary prevention. Statins prevent cardiovascular events in patients at risk. However, despite the proven efficacy and safety of statins, relevant side effects exist and should be considered when treating patients.

Key words: *statin; cardiovascular disease; hypercholesterolaemia*

Introduction

For centuries the quest for eternal life as well as the consequences of human curiosity have been a guiding theme in literature and philosophy. Innumerable heroes have been searching for the Holy Grail as the symbol of everlasting happiness, health and youth but have failed to find it, while Pandora's curiosity was responsible for opening the box filled with all evil that spread throughout the world.

Cardiovascular disease due to thrombosis and atherosclerosis of the arterial vessel wall remains the foremost cause of premature mortality, morbidity, and disability in Western societies and – increasingly – in developing countries [1]. Cardiovascular risk factors such as arterial hypertension, diabetes mellitus, and hyperlipidaemia account for a large part of the burden of disease and are the main targets for primary and secondary prevention in cardiovascular medicine. Drugs to slow down the development of atherosclerosis and to attenuate the effects of cardiovascular events are subject to intense research. In this respect, statins are among the most powerful inventions to prevent cardiovascular events in patients at risk. However, despite the proven efficacy and safety of statins, relevant side effects exist and should be considered when treating patients. This review intends to review efficacy and safety, current indications, and future directions in statin therapy.

Statins: history and mode of action

In 1976, the first statin, the so-called "compactin" (mevastatin), was synthesised in Japan [2]. Since then, seven compounds have entered the market. Lovastatin became the first commercially available statin in 1987, followed by simvastatin, pravastatin, atorvastatin, rosuvastatin, and pitavastatin (table 1) [3]. Cerivastatin had to be withdrawn from the market in 2001 due to side effects [4].

Statins are competitive inhibitors of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase that is responsible for a rate-limiting step in cholesterol biosynthesis at the cellular level [5, 6]. By inhibiting the conversion of HMG-CoA to mevalonic acid, statins promote the expression of low-density lipoprotein (LDL)-receptors on hepatocytes, thus lowering both LDL and total serum cholesterol by increased uptake from the circulation [6]. With the maximal approved doses of currently used statins, an average LDL reduction of 31–63% can be achieved (table 1) [7]. To a lesser extent, statins lower the levels of very low-density lipoproteins (VLDL), mainly by inhibiting the production of apolipoprotein B in the liver [8], and increase the levels of high-density lipoproteins (HDL) [6, 9]. Most statins are metabolised by the hepatic cytochrome P450 system with the potential for drug-drug interactions.

In large trials, the extent of LDL reduction was directly proportional to the reduction in cardiovascular risk [10]. While the primary beneficial effects of statins are thought to be a consequence of their lipid-lowering qualities, there may be additional, so-called "pleiotropic" effects independent of serum cholesterol levels [11]. This notion is based on the observation that statins, in addition to lowering cholesterol synthesis, inhibit the genesis of isoprenoid intermediates. These latter are important lipid attachment molecules for post-translational modification of a variety of proteins that play a crucial role in the regulation of cell growth and differentiation, gene expression, cytoskeletal assembly and cell motility, protein and lipid trafficking, nuclear transport, inflammation, and host defence [11, 12]. Moreover, it was demonstrated that statins improve endothelial function and promote cardioprotective effects via anti-oxidant, anti-inflammatory, anti-thrombotic as well as beneficial plaque-modifying effects (table 2). Statins show an immediate inhibition of smooth-muscle cell proliferation and stimulation of re-endothelialisation [13].

Primary and secondary prevention of cardiovascular events

Application of statins represents an effective treatment of hypercholesterolaemia and is efficient in primary and secondary prevention of cardiovascular events in patients at

high cardiovascular risk [14, 15]. The application of high doses of statins have also entered guidelines for acute coronary syndromes [16].

Large trials have shown a direct association between lower levels of serum LDL cholesterol and decreased cardiovascular event rates such as myocardial infarction, need for revascularisation, and ischaemic stroke [10, 17, 18]. Data from large populations show that a 10% reduction in total plasma cholesterol was associated with an impressive 25% reduction in coronary artery disease incidence after 5 years, while a reduction of LDL cholesterol of 1 mg/L was associated with a 20% decreased incidence of cardiovascular events [10]. This effect has been demonstrated for both primary and secondary prevention since lipid lowering with statins proved efficacy in decreasing cardiovascular event rates in populations with and without known coronary artery disease [10, 18].

Hypercholesterolaemia

For most forms of hypercholesterolaemia such as heterozygous and homozygous familial hypercholesterolaemia, primary moderate hypercholesterolaemia, familial dysbetalipoproteinaemia, familial combined hyperlipidaemia, and diabetic and nephrotic dyslipidaemia, statins are the treatment of choice [6, 15]. Due to the fact that hypercholesterolaemia is one of the key risk factors for cardiovascular atherosclerotic disease, lipid-lowering therapy is indicated in patients with an elevated baseline risk. In clinical practice, the decision to initiate a lipid-lowering therapy and the choice of drug should be based on the estimated future cardiovascular risk, although this approach is not based on hard evidence. To estimate the individual risk of a patients, several score systems can be used; one of the most frequently used methods to assess the risk of future cardiovascular events was derived from the Systemic Coronary Risk Estimation (SCORE) project [19]. SCORE provides an estimate of the 10-year risk of fatal cardiovascular disease in a general population without overt coronary artery disease, diabetes mellitus, chronic kidney disease, or very high levels of individual risk factors. SCORE risk estimates are based on risk factors such as age, gender, smoking, systolic blood pressure, and total cholesterol and are displayed in so-called SCORE charts (www.heartscore.org). In these guidelines, lipid-lowering therapy is recommended in patients at a certain baseline risk depending on their measured lipid levels. Other scores are the Prospective Cardiovascular Münster Heart Study (PROCAM) risk score (www.chd-taskforce.de/pdf/sk_procam_07d.pdf) based on LDL- and HDL-cholesterol, triglycerides, systolic blood pressure, fasting glucose, diabetes mellitus, age, smoking, antihypertensive treatment, and family history of coronary artery disease, or the Framingham score (www.framinghamheartstudy.org/risk/coronary.html) based on LDL-, HDL- and total cholesterol, systolic and diastolic blood pressure, age, smoking, and diabetes mellitus, that both give an estimate of the 10-year risk for developing coronary artery disease.

Primary prevention

In several large meta-analyses, the effect of statins on mortality in primary prevention populations was assessed [20–24]. Actually, the most recent reports with the largest number of events report a clear mortality benefit of statin therapy in individuals without overt coronary artery disease [23, 25]. The finding of these meta-analyses is in concordance with the results of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) [26]. In this large, prospective, controlled randomised trial, 17,802 apparently healthy patients >50 years of age with normal cholesterol levels but elevated levels of C-reactive protein (CRP) >2.0 mg/L were randomised to statin treatment with rosuvastatin vs. placebo. After a mean follow-up of 1.9 years, the trial was stopped early on recommendation of the trial's Data Safety Monitoring Board. Results were impressive with a hazard ratio of 0.56 (95% confidence interval 0.46–0.69; p <0.00001) for the combined primary end point of myocardial infarction, stroke, arterial revascularisation, hospitalisation for unstable angina, or death from cardiovascular causes. Therefore, the decision to initiate statin therapy in primary prevention should be based on the estimate of individual cardiovascular risk. Currently accepted targets in-

Table 1: Current HMG-CoA-inhibitors.

Compound	Metabolism	Dose Range (mg)	Max. LDL Reduction at Highest Dose (%)
Lovastatin	CYP3A4	20–80	40
Simvastatin	CYP3A4	10–80	46
Pravastatin	None (sulphation)	20–80	34
Fluvastatin	CYP2C9, 2C8, 3A4	40–80	31
Atorvastatin	CYP3A4	10–80	57
Rosuvastatin	Minimal (CYP2CP, 2C19)	5–40	63
Pitavastatin	Minimal (CYP2C9, 2C8)	2–4	41

Table 2: Postulated pleiotropic effects.

Effect
Improvement of endothelial function: expression and activity of endothelial nitric oxide synthase (eNOS)
Anti-oxidant effect: prevention of oxidative stress and atherosclerosis
Anti-inflammatory effect: endothelial cell and leucocyte adhesion molecules
Plaque modifying effect: macrophage activation and proliferation, smooth muscle cell proliferation and apoptosis
Anti-thrombotic effect: fibrinogen-thrombocyte interaction, coagulation system, fibrinolytic balance
Anti- and proangiogenic effects: inhibition and promotion of neorevascularisation
Cardioprotective effect: prevention of myocardial hypertrophy and fibrosis, cardiomyocyte protection

clude a LDL cholesterol goal <1.8 mmol/l in patients at very high, <2.5 mmol/l in patients at high cardiovascular, and <3.0 mmol/l in patients at moderate cardiovascular risk [15]. In contrast, the way patients were risk-stratified in JUPITER, i.e., by selecting healthy patients >50 years of age with normal cholesterol levels but elevated levels of CRP, is much more straight-forward; therefore, an elevated CRP may also be used as a risk stratification tool. Of note, in JUPITER the number needed to treat for the primary endpoint over 5 years was 25 [27].

Secondary prevention

The broadest evidence for the beneficial effect of statin therapy has been established in patients with known cardiovascular diseases such as coronary artery disease, peripheral arterial occlusive disease, and cerebrovascular disease since these patients are at highest risk of recurrent events [14]. This notion has been corroborated by data from a large meta-analysis of 26 trials in 170'000 patients where benefit was largest in high-risk populations [10]. The treatment of patients with known coronary artery disease with statins was associated with a marked decrease in all-cause mortality (risk ratio 0.90, 95% confidence interval 0.87–0.93; p <0.0001), mortality due to coronary artery disease (risk ratio 0.80, 99% confidence interval 0.74–0.87; p <0.0001), and mortality due to other cardiac causes (risk ratio 0.89, 99% confidence interval 0.81–0.98; p = 0.002), while no significant effect was seen on deaths due to stroke (risk ratio 0.96, 95% confidence interval 0.84–1.09; p = 0.5) or other vascular causes (risk ratio 0.98, 99% confidence interval 0.81–1.18; p = 0.8) [10]. Specifically, statin therapy has been shown to be beneficial even in the absence of overt coronary artery disease in patients with diabetes and chronic kidney disease since these patients have an increased baseline risk for cardiovascular events already [15].

Side effects

Unfortunately, there is no effective treatment without side effects. However, statins have a favourable safety and efficacy profile with a low rate of serious adverse effects. The most frequent side effects of statins are muscle and liver toxicity and gastrointestinal discomfort [3]. Moreover, important drug-drug interactions have to be taken into account (table 3).

The most important side effect of statins is myopathy, i.e., a serum creatine kinase level more than 10 times the upper limit of normal with unexplained muscle weakness or pain, and rhabdomyolysis, i.e., unexplained muscle pain or weakness with a serum creatine kinase level more than 40 times the upper limit of normal. Patients on higher doses of statins as well as patients on concomitant medication with the potential for drug-drug interaction are at increased risk. Data from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) that treated survivors of myocardial infarction with high- vs. low-dose simvastatin showed that patients treated with higher simvastatin doses had a higher incidence of side effects [28], possibly due to drug-drug interactions between simvastatin and other drugs such as vitamin K antagonists, amiodarone, diltiazem, and amlodipine. Therefore, the US Food and Drug Administration (FDA) issued a safety labelling change for simvastatin [7]. As noted earlier, cerivastatin was withdrawn from the market due to a high rate of rhabdomyolysis [4]. Routine measurement of creatine kinase levels in patients on statins is not recommended unless muscle weakness or bilateral proximal muscle pain with no obvious cause are reported. In these patients, statin therapy and interacting drugs should be stopped immediately and serum levels controlled. After normalisation of serum levels, statin therapy can be restarted with another compound at a lower dosage with close monitoring of creatine kinase levels [3]. Of note, muscle pain can occur in the absence of elevated creatine kinase and might lead to non-compliance of patients regarding treatment adherence. Other side effects, such as elevations in liver enzymes and gastrointestinal discomfort, are harmless. Regarding liver enzymes, mostly alanine or aspartate transaminases have been reported to be elevated in the initial 6 months of statin treatment in large trials. However, for most statins at standard doses, no routine control of transaminase levels is recommended after the start of treatment; only for fluvastatin, atorvastatin, rosuvastatin, and pitavastatin and all statins at higher doses routine controls should be done despite the lack of evidence [3].

Statin therapy is associated with increased rates of diabetes mellitus accounting for a 9% increased risk of developing diabetes mellitus [27, 29]. This risk seems to be dose-dependent [30]. The relevance of this finding is not clear yet, but could be important since diabetes mellitus is another key risk factor for the development of atherosclerosis.

In addition, it is important to emphasise that statins do not increase non-cardiovascular mortality or the incidence of intercurrent cancer [10]. These findings refute previous notions where an increased risk of cancer was assumed [31]. The pseudo-association of statin therapy and increased non-cardiovascular mortality may be explained by the fact that cholesterol-lowering therapy decreases cardiovascular death rates at a much higher level than other reasons of death.

Table 3: Side effects of statin therapy (without cerivastatin).

Effect (incidence/increased incidence)
Muscle toxicity (myopathy 0.1–0.9%, rhabdomyolysis 0–0.4%)
Liver enzyme elevation (0.11–3.3%)
Diabetes mellitus (9%)
Gastrointestinal effects (diarrhoea, abdominal pain, nausea)

Table 4: Drug-drug interactions.

Interaction
Fibrates (concomitant use with statins may lead to severe rhabdomyolysis)
Antiarrhythmics (amiodarone, diltiazem)
Vitamin K antagonists
Amlodipine
Antifungals (e.g., ketoconazole)
Macrolide antibiotics (e.g., clarithromycin)
Antidepressants (nefazodon)
HIV protease inhibitors
Ciclosporin (fluvastatin may be used), everolimus, tacrolimus

Conclusion

Based on substantial evidence, statins are effective drugs in the treatment of hyperlipidaemia and the prevention of cardiovascular events. Recent data show that even patients without elevated lipid levels and overt coronary artery disease might benefit from a primary prevention approach. On the other hand, statins are safe and have few side effects. Specifically, muscle toxicity with myopathy and rhabdomyolysis is rare and mostly occurs in patients on higher statin doses and on drugs that interact at the level of hepatic metabolism. Routine monitoring of muscle and hepatic enzymes is not mandatory and is restricted to patients with symptoms or on high statin doses and/or other medication with a drug-drug interaction potential.

Funding / potential competing interests: No financial support and no other potential conflict of interest relevant to this article was reported.

Correspondence: *Raban Jeger, MD, Cardiology, University Hospital, Petersgraben 4, CH-4031 Basel, Switzerland, rjeger[at]uhbs.ch*

References

1 Allender S, Scarborough P, Peto V, Rayner M, Leal J, Luengo-Frenandez R, et al. European cardiovascular disease statistics 2008. Brussels, European Heart Network. 2008, 2008.

2 Endo A. A gift from nature: The birth of the statins. Nat Med. 2008;14:1050–2.

3 Armitage J. The safety of statins in clinical practice. Lancet. 2007;370:1781–90.

4 Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. Curr Control Trials Cardiovasc Med. 2001;2:205–7.

5 Brown MS, Goldstein JL. Multivalent feedback regulation of hmg coa reductase, a control mechanism coordinating isoprenoid synthesis and cell growth. J Lipid Res. 1980;21:505–17.

6 Grundy SM: Hmg-coa reductase inhibitors for treatment of hypercholesterolemia. N Engl J Med. 1988;319:24–33.

7 Egan A, Colman E. Weighing the benefits of high-dose simvastatin against the risk of myopathy. N Engl J Med. 2011;365:285–7.

8 Arad Y, Ramakrishnan R, Ginsberg HN. Effects of lovastatin therapy on very-low-density lipoprotein triglyceride metabolism in subjects with combined hyperlipidemia: Evidence for reduced assembly and secretion of triglyceride-rich lipoproteins. Metabolism. 1992;41:487–93.

9 Chapman M. Are the effects of statins on hdl-cholesterol clinically relevant? Eur Heart J. Supplements 2004;6(Suppl. C):C58–C63.

10 Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of ldl cholesterol: A meta-analysis of data from 170000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.

11 Bonetti PO, Lerman LO, Napoli C, Lerman A. Statin effects beyond lipid lowering – are they clinically relevant? Eur Heart J. 2003;24:225–48.

12 Goldstein JL, Brown MS. Regulation of the mevalonate pathway. Nature. 1990;343:425–30.

13 Walter DH. Insights into early and rapid effects of statin therapy after coronary interventions. Curr Pharm Des. 2004;10:369–73.

14 Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, et al., (ESC) ESoC, (EACPR) EAfCPaR, Nursing CoC, (EASD) EAfSoD, (IDF-Europe) IDFE, (EUSI) ESI, (ISBM) ISoBM, (ESH) ESoH, (ESGP/FM/WONCA) ESoGPFM, (EHN) EHN: European guidelines on cardiovascular disease prevention in clinical practice: Executive summary. Fourth joint task force of the european society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil. 2007;14(Suppl 2):E1–40.

15 Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, et al., Rehabilitation EAfCP, Committees ECfPGC-a-: Esc/eas guidelines for the management of dyslipidaemias: The task force for the management of dyslipidaemias of the european society of cardiology (esc) and the european atherosclerosis society (eas). Eur Heart J. 2011;32:1769–818.

16 Vale N, Nordmann AJ, Schwartz GG, de Lemos J, Colivicchi F, den Hartog F, et al. Statins for acute coronary syndrome. Cochrane Database Syst Rev 2011:CD006870.

17 Steinberg D. Thematic review series: The pathogenesis of atherosclerosis. An interpretive history of the cholesterol controversy, part v: The discovery of the statins and the end of the controversy. J Lipid Res. 2006;47:1339–51.

18 Ray KK, Cannon CP. Pathological changes in acute coronary syndromes: The role of statin therapy in the modulation of inflammation, endothelial function and coagulation. J Thromb Thrombolysis. 2004;18:89–101.

19 Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al., group Sp: Estimation of ten-year risk of fatal cardiovascular disease in europe: The score project. Eur Heart J. 2003;24:987–1003.

20 Thavendiranathan P, Bagai A, Brookhart MA, Choudhry NK. Primary prevention of cardiovascular diseases with statin therapy: A meta-analysis of randomized controlled trials. Arch Intern Med. 2006;166:2307–13.

21 Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D. Primary prevention of cardiovascular mortality and events with statin treatments: A network meta-analysis involving more than 65,000 patients. J Am Coll Cardiol. 2008;52:1769–81.

22 Ray KK, Seshasai SR, Erqou S, Sever P, Jukema JW, Ford I, et al. Statins and all-cause mortality in high-risk primary prevention: A meta-analysis of 11 randomized controlled trials involving 65,229 participants. Arch Intern Med. 2010;170:1024–31.

23 Tonelli M, Lloyd A, Clement F, Conly J, Husereau D, Hemmelgarn B, et al. Efficacy of statins for primary prevention in people at low cardiovascular risk: A meta-analysis. CMAJ. 2011;183:E1189–1202.

24 Taylor F, Ward K, Moore TH, Burke M, Davey Smith G, Casas JP, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2011:CD004816.

25 Barsness GW, Buller C, Ohman EM, Schechter E, Pucillo A, Taylor MA, et al. Reduced thrombus burden with abciximab delivered locally before percutaneous intervention in saphenous vein grafts. Am Heart J. 2000;139:824–9.

26 Ridker P, Danielson E, Fonseca F, Genest J, Gotto AJ, Kastelein J, et al. Rosuvastatin to prevent vascular events in men and women with elevated c-reactive protein. N Engl J Med. 2008;359:2195–207.

27 Ridker PM, MacFadyen JG, Fonseca FA, Genest J, Gotto AM, Kastelein JJ, et al.; JUPITER Study Group: Number needed to treat with rosuvastatin to prevent first cardiovascular events and death among men and women with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin (JUPITER). Circ Cardiovasc Qual Outcomes. 2009;6:616–23.

28 Armitage J, Bowman L, Wallendszus K, Bulbulia R, Rahimi K, Haynes R, et al., Group SotEoARiCaHSC: Intensive lowering of ldl cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: A double-blind randomised trial. Lancet. 2010;376:1658–69.

29 Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: A collaborative meta-analysis of randomised statin trials. Lancet. 2010;375:735–42.

30 Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: A meta-analysis. JAMA. 2011;305:2556–64.

31 Neaton JD, Blackburn H, Jacobs D, Kuller L, Lee DJ, Sherwin R, et al. Serum cholesterol level and mortality findings for men screened in the multiple risk factor intervention trial. Multiple risk factor intervention trial research group. Arch Intern Med. 1992;152:1490–500.