Benefits of statins beyond lipid lowering

M.W. Merx¹,², C. Weber²

¹Department of Medicine, Division of Cardiology, Pulmonary Diseases and Vascular Medicine, RWTH Aachen University, Aachen, Germany
²Institute of Molecular Cardiovascular Research (IMCAR), RWTH Aachen University, Aachen, Germany

Increasing evidence has accumulated suggesting that inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, or statins, have therapeutic ‘pleiotropic’ effects independent of cholesterol lowering. These include anti-inflammatory and antioxidative properties, improvement of endothelial function and increased nitric oxide bioavailability. In addition to elucidating underlying mechanisms, research on ‘pleiotropic’ effects of statins has added a wide scope of potential targets for statin therapy ranging from acute coronary syndromes (ACSs) to renal failure, neurologic disorders and infectious diseases to name just a few.

Introduction

Two-third of the body's cholesterol is synthesized in the liver with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase as the rate-limiting enzyme of the mevalonate pathway for cholesterol biosynthesis [1]. Owing to their structural homology to HMG-CoA, statins competitively inhibit HMG-CoA reductase activity in a dose-dependent fashion [2]. This reduced cholesterol synthesis in conjunction with negative-feedback low-density lipoprotein (LDL) receptor upregulation leads to markedly reduced serum LDL levels. Since the approval for clinical use in humans of lovastatin as the first statin, several statins have become commercially available including pravastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin (with-drawn in 2001), pitavastatin and rosuvastatin. While all these statins share HMG-CoA reductase inhibition as their common mechanism of action, they differ in absorption, affinity, binding, solubility and excretion (for details see [3]). Apart from causing variations in efficacy of cholesterol lowering between the agents, differences in these pharmacological properties might also be relevant with respect to the so-called pleiotropic effects of statins.

Statins were developed for, and currently represent the mainstay of, dyslipidemia treatment. Ample evidence supports the use of statins to lower cholesterol for primary and secondary prevention of coronary artery disease (CAD). The Scandinavian Simvastatin Survival Study (4S) demonstrated as early as 1994 that statin therapy could reduce the all-cause mortality rate in a secondary prevention population [4]. These results were subsequently confirmed by several landmark clinical trials (CARE [5] and LIPID [6]). In 1995 the West of Scotland Coronary Prevention Study (WOSCOP [7]) extended the benefit of statin treatment to primary prevention by pravastatin application in hypercholesterolic men. Lovastatin was used in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS [8]) to further extend the benefit of primary prevention to a healthy, mixed gender cohort. Recently, the investigators of the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL [9]) were able to demonstrate that progression of atherosclerosis can be abrogated by high-dose atorvastatin treatment (80 mg) compared to moderate-dose pravastatin therapy (40 mg) which resulted in 2.7% progression of coronary atheroma burden over...
18 months. Currently ongoing is the “Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER),” a randomized, double-blind, placebo-controlled primary prevention trial of statin therapy among persons with average to low levels of LDL cholesterol who are at increased cardiovascular risk as assessed by elevated plasma concentrations of the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP). With a total of 17,802 persons recruited, the JUPITER trial should broaden our understanding of statin therapy and inflammation, and provide information on primary prevention among patients who do not currently qualify for lipid-lowering therapy.

Over the past years, increasing evidence has accumulated suggesting that inhibitors of HMG-CoA reductase, or statins, have therapeutic ‘pleiotropic’ effects independent of cholesterol lowering (see Fig. 1). These include anti-inflammatory and antioxidative properties, improvement of endothelial function and increased endothelial nitric oxide synthetase expression and nitric oxide bioavailability, which might contribute to the therapeutic benefit observed with statin therapy. Notably, important immunomodulatory effects of statins have been demonstrated to be independent of lipid lowering [11].

**Statin mechanisms of action beyond lipid lowering**

Several pleiotropic effects of statins appear to be mediated via interference with the synthesis of mevalonate metabolites (nonsteroidal isoprenoid products). Blockade of the mevalonate pathway has been shown to suppress T-cell responses [12] to reduce expression of class II major histocompatibility complexes on antigen-presenting cells [11] and to inhibit chemokine synthesis in peripheral blood mononuclear cells [13]. Furthermore, CD11b integrin expression and CD11b-dependent adhesion of monocytes have been found to be attenuated by initiating statin treatment in hypercholesterolemic patients [14]. In this context, Yoshida et al. [15] have reported that statins reduce the expression of both monocytic and endothelial adhesion molecules, for example, the integrin leukocyte function-associated antigen-1 (LFA-1), via an inhibition of Rho GTPases and in particular their membrane anchoring by isoprenylation/geranylation. This inhibition of the GTPases Rho or Rac and their downstream effects have also been found to underlie improved endothelial function, reduced smooth muscle cell contractility, downregulation of endothelin function, attenuated production of reactive oxygen species production [16]. In addition, mechanisms for anti-inflammatory actions of statins unrelated to the isoprenoid metabolism have been identified, such as the capacity of some statins to bind to the regulatory site in the LFA-1 I-domain and thus act as direct antagonists of LFA-1 [17].

Finally, long-term therapy with statins has been shown to associate dose-dependently with decreased numbers of endothelial progenitor cells in patients with angiographically documented CAD, possibly related to an anti-inflammatory action on mononuclear cell populations [18]. Besides these multifaceted anti-inflammatory effects, statins may interfere with the activation of the coagulation cascade, as illustrated by the suppression of lipopolysaccharide-induced monocyte tissue factor in vitro [19] and inhibition of plasminogen activator inhibitor type-I expression [16]. These ‘pleiotropic’
effects have added a wide scope of potential targets for statin therapy ranging from acute coronary syndromes (ACSs) to renal failure, neurologic disorders and infectious diseases to name just a few.

Statins and ACS
While the benefit of statin therapy in patients with stable CAD is clearly recognized, the positive impact of statin therapy initiation immediately following ACS occurrence has emerged only recently. Comprising ST-elevation (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) as well as unstable angina (UA), ACS patients frequently require intensive care treatment and are at high risk for recurrent coronary events, sudden death and all-cause mortality. The stabilization of vulnerable lesions is a crucial aspect in preventing these events following ACS. Despite significant advances in antiplatelet and antithrombotic therapy, these therapeutic options alone do not appear to suffice in treating the unstable plaque. Through their cholesterol lowering and pleiotropic effects, statins are viewed as important contributors to plaque stabilization (for an excellent review see Libby and Aikawa [20]). Several retrospective and observational studies have suggested that initiating statin therapy immediately after an ACS is associated with significantly reduced rates of recurrent coronary events and death [21–28]. To date, two smaller [29,30] and three large-scale, randomized, controlled trials have followed up on these observational studies. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) [31] trial was the first one to demonstrate a reduced rate of recurrent cardiac events by statin therapy. In this study, 3086 patients with UA or non-Q-wave infarction were randomized within 24–96 hours after hospital admission to receive either 80 mg of atorvastatin or placebo in addition to state of the art therapy for four months after ACS. The primary endpoint of the trial — death, cardiac arrest, MI, or worsening UA requiring emergency hospitalization at 16 weeks — showed a relative risk reduction of 16% (95% CI, 0–30; P = 0.048; absolute risk reduction 2.6%). Further analysis of the MIRACL data [32] revealed the observed benefit to be unrelated to both baseline and achieved LDL levels. The Pravastatin or Atorvastatin Evaluation and Infection Therapy Trial (PROVE IT [33]) compared intensive lipid-lowering therapy with atorvastatin 80 mg to conventional lipid lowering with pravastatin 40 mg in 4162 men and women. The patients enrolled had been hospitalized for an ACS within the preceding ten days. The benefit derived from intensive lipid lowering versus conventional lipid lowering on top of background evidence-based ACS therapy (including antiplatelet therapy, β-blockers and ACE inhibitors in a large majority of patients) accumulated to a relative risk reduction of 16% (95% CI, 5–26; P = 0.005; absolute risk reduction, 3.9%; mean follow-up 24 months).

Inconsistent with these findings, the Aggrastat to Zocor (A–Z [34]) trial did not demonstrate superiority for the intensive statin regimen. The observed benefit in MIRACL being unrelated to LDL levels [32] as well as the similar LDL reduction in positive and negative trials (62 mg/dl in A–Z, 63 mg/dl in MIRACL) suggest that event reduction in the positive trials might not have been entirely attributable to LDL-C reduction, but also derived from suppressed inflammatory response as reflected by hsCRP levels decreased by 34% and 38% in MIRACL and PROVE IT, respectively, with hsCRP reduced by only 17% in the A–Z trial. On the basis of the findings from these three large randomized trials, Nissen [35] elegantly speculates that the early benefits of statin therapy may be caused largely by anti-inflammatory effects, whereas the delayed benefits are more probably lipid modulated. However, Robinson et al. [36] recently produced a meta-analysis of statin trials suggesting that an approximate one-to-one relationship exists between %-degree of LDL-C reduction and %-reduction of recurrent events.

Statins and heart failure
In rat models of heart failure, statins reduce collagen, enhance reverse myocardial remodeling and prolong survival [37]. In conjunction with further animal models and clinical observational data, these findings have led to randomized trials. Sola et al. have reported a one-year, prospective, double-blind, placebo-controlled study of atorvastatin (20 mg/d) in 108 patients with New York Heart Association (NYHA) class II–IV nonischemic heart failure and ejection fractions (EFs) below 35% [38]. EF increased from 33% to 37% in the treatment group while EF decreased from 33% to 31% in the controls. The improved EF was associated with reductions in serum CRP, interleukin-6 and TNF receptor in the atorvastatin group. These results could not be confirmed by the recently published large CORONA study which enrolled a total of 5011 patients at least 60 years of age with NYHA class II, III, or IV ischemic, systolic heart failure randomly assigned to receive 10 mg of rosvastatin or placebo/day [39]. While patients in the rosvastatin group had decreased levels of LDL (reduced by 45.0%; P < 0.001) and of hsCRP (reduced by 37.1%; P < 0.001), there were no significant differences between the two groups in the coronary outcome or death from cardiovascular causes. However, in a prespecified secondary analysis, there were fewer hospitalizations for cardiovascular causes in the rosvastatin group (2193) than in the placebo group (2564) (P < 0.001). Very recently the results of the Gruppo Italiano per lo Studio della Sopravvivenza nel’Insufficienza Cardiaca Heart Failure Study (GISSI-HF), a randomized trial in which patients with heart failure NYHA II–IV, irrespective of left-ventricular EF and cause of heart failure, received either rosvastatin (n = 2285) or placebo (n = 2289), were reported [40]. During a mean follow-up of 3.9 years, rosvastatin had no effect on the primary or secondary endpoints of the study. Furthermore, in GISSI-HF several clinically relevant subgroups, such as preserved
versus reduced EF, ischemic versus nonischemic origin, NYHA class, age, cholesterol levels and diabetic status were analyzed without detectable outcome improvement in any of the subgroups. So while statin treatment was demonstrated to be safe even in this high-risk population, both recent large-scale studies taken together imply that statins are not indicated for chronic heart failure.

**Statins and renal disease**

Studies in experimental models of kidney disease on the anti-inflammatory and immunologic effects of statins as well as post hoc analysis of randomized cardiovascular statin trials that included patients with chronic kidney disease (CKD) have demonstrated very promising data (for a detailed review see [41]). In a prospective, controlled, open label study, 56 patients with CKD, proteinuria and hypercholesterolemia were randomized to atorvastatin or placebo [42]. At one year, the atorvastatin group experienced a decrease in urine protein excretion from 2.2 to 1.2 g/24 hours (P < 0.01) with no significant change in the placebo group. Similarly, creatinine clearance decreased in the placebo group over the one-year study period while no significant drop in creatinine clearance was observed in the atorvastatin-treated patients. A currently ongoing multinational, randomized trial is evaluating the effects of rosuvastatin and atorvastatin on urinary protein excretion over one year in CKD patients with type 1 or 2 diabetes (PLANET I, NCT00296374) and without diabetes (PLANET II, NCT00296400) with moderate proteinuria and hypercholesterolemia. While several small studies have demonstrated cardiovascular risk improvement in patients with end stage renal disease (ESRD) [41], the recently published multicenter, randomized, double-blind Deutsche Diabetes Dialyse Studie (4D) demonstrated no mortality benefit in 1255 type II diabetic patients with ESRD. Thus, the cardiovascular benefits of statins in ESRD patients remain unclear and the results of the AURORA (NCT00240331) study in more than 2750 patients with ESRD are eagerly awaited.

**Statins and neurologic disorders**

In analogy to their success in the reduction of cardiovascular events, statins have been suggested to reduce the risk of cerebrovascular accidents. In the Heart Protection Study, 20,536 patients with and without a prior history of stroke were treated with simvastatin 40 mg/d and experienced 25% fewer strokes compared to placebo (P < 0.0001) [43]. In contrast, the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial showed no significant effect on stroke prevention [44]. Recently, the SPARCL trial randomly assigned 4731 patients who had had a stroke or TIA within one to six months before study entry, had LDL cholesterol levels of 100–190 mg/dl, and had no known coronary heart disease to double-blind treatment with 80 mg of atorvastatin/day or placebo. The primary end point was a first nonfatal or fatal stroke. During a median follow-up of 4.9 years, 265 patients (11.2%) receiving atorvastatin and 311 patients (13.1%) receiving placebo had a fatal or nonfatal stroke (five-year absolute reduction in risk, 2.2%; adjusted hazard ratio (HR), 0.84; 95% confidence interval, 0.71–0.99; P = 0.03; unadjusted P = 0.05) [45]. However, the rate of hemorrhagic stroke was slightly increased in the atorvastatin group. In a secondary analysis of the SPARCL data, achieving a decrease in LDL levels ≥50% as compared with having no change or an increase in LDL-C, was associated with a greater reduction in the risk of stroke and major coronary events with no increase in brain hemorrhages [46].

In addition to cerebrovascular accidents, the effects of statins on cognitive decline have been studied. Neither the PROSPER [44] nor the Heart Protection Study [43] demonstrated a statin-derived benefit on cognitive function. With respect to Alzheimer’s disease, a small randomized, double-blind trial in 63 patients demonstrated a positive effect on the Alzheimer Disease Assessment Scale-Cognitive performance that occurred after six months of 80 mg/d atorvastatin therapy compared with placebo. This positive effect was more prominent among individuals entering the trial with (i) milder disease (higher MMSE scores), (ii) cholesterol levels above 200 mg/dl or (iii) if they harbored an apolipoprotein-E-4 allele compared with participants not responding to atorvastatin treatment. Individuals in the placebo group tended to experience more pronounced deterioration if their cholesterol levels exceeded 200 mg/dl or they harbored an apolipoprotein-E-4 allele [47]. Results from the larger CLAP study (NCT00053599), assessing the safety and effectiveness of simvastatin to slow the progression of Alzheimer’s disease should become available soon.

As cerebrocholesterol is increased in patients with multiple sclerosis (MS), statins have been applied to animal models of MS and Vollmer et al. were able to demonstrate that oral simvastatin (80 mg/d) applied to 30 individuals with relapsing–remitting MS reduced the mean number of gadolinium-enhancing lesions at months 4, 5 and 6 of treatment as compared with the mean number of lesions noted on pretreatment brain MRI scans. Several large randomized trials are currently under way and will hopefully substantiate these preliminary findings.

**Statins and infectious disease**

Given the strong impact of statins on inflammation, statins might represent a welcome enforcement in the battle against severe infectious diseases, such as sepsis. Consequently, several investigators have evaluated the role of statins in the prevention and treatment of sepsis. In a retrospective analysis Liappis et al. [48] have demonstrated a reduced overall and attributable mortality in patients with bacteremia who were concomitantly treated with statins. Pretreatment with simvastatin has been shown to profoundly improve survival in a
polimicrobial murine model of sepsis by the preservation of cardiovascular function and inhibition of inflammatory alterations [49]. Encouraged by these findings, the same model was employed to successfully treat sepsis in a clinically feasible fashion, that is, treatment was initiated several hours after the onset of sepsis. With different statins (atorvastatin, pravastatin and simvastatin) being effective, the therapeutic potential of statins in sepsis appears to be a class effect [50].

Recently, Steiner et al. [51] observed that pretreatment with simvastatin can suppress the inflammatory response induced by lipopolysaccharide in healthy human volunteers. Furthermore, in a prospective observational cohort study in patients with acute bacterial infections performed by Almog et al. [52] previous treatment with statins was associated with a considerably reduced rate of severe sepsis and intensive care unit admissions. 361 patients were enrolled in this study and 82 of these patients had been treated with statins for at least four weeks before their admission. Severe sepsis developed in 19% of patients in the non-statin group compared to only 2.4% in patients who were on statins. The ICU admission rates were 12.2% for the non-statin group and 3.7% for the statin group. Owing to the number of patients enrolled, this study was not powered to detect differences in mortality although the large effect on sepsis rate and ICU admission were at least suggestive. As recent development in this field, Hackam et al. [53] have produced an impressive observational study by initial evaluation of 141,487 cardiovascular patients resulting in a well-paired and homogenous study cohort of 69,168 patients after propensity-based matching. Drawing from this solid base, Hackam and coauthors were able to support the conclusion that statin therapy is associated with a considerably decreased rate of sepsis (HR 0.81; 95% CI 0.72–0.90), severe sepsis (HR 0.83; 95% CI 0.70–0.97) and fatal sepsis (HR 0.75; 95% CI 0.61–0.93). This protective effect prevailed at both high and low statin doses and for several clinically important subpopulations such as diabetic and heart failure patients. Similarly, a large prospective observational study from Israel followed 11,490 patients with atherosclerotic diseases, stratified to whether they had received statins in the final month before follow-up termination or not, reported a reduced infection-related mortality (0.9% in the statin group versus 4.1% in the nonstatin group), reflecting a relative risk of 0.22 (95% CI, 0.17–0.28) [54].

Beyond their immunomodulatory functions, statins have been shown to exert direct antibacterial and antiviral effects. As a discussion of these effects would be beyond the scope of this review, the reader is kindly referred to the excellent summaries available on the topic (e.g. Terblanche et al. [56] and Fedson [57]).

**Conclusion**

The available evidence suggests that the pleiotropic effects of statins lend themselves to a wide spectrum of disease treatment and disease prevention. To what extent these anti-inflammatory and immunomodulatory effects are truly pleiotropic or mediated by decreased LDL levels remains a matter of interesting scientific debate that will probably not be answered congruently for each individual condition studied. A few published and many more ongoing randomized clinical trials are now beginning to test the intriguing hypotheses generated from experimental, retrospective and observational data.

This enthusiasm not withstanding caution should prevail, as statins may have detrimental effects in distinct subsets of patients, and using statins in patients with nonestablished indications must be accompanied by meticulous monitoring of unexpected side effects and well-designed randomized, controlled clinical trials.

**Conflict of interest statement**

No conflicts of interest to declare.

**Acknowledgements**

This work was supported by the Deutsche Forschungsgemeinschaft (Me1821/2, Me1821/3, We1913/11, FOR809) and the Interdisciplinary Center for Clinical Research (IZKF Biomat.).

**References**

8. Downs, J.R. et al. (1998) 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 279, 1615–1622
9 Nissen, S.E. et al. (2004) Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 291, 1071–1080
10 Ridker, P.M. et al. (2007) Baseline characteristics of participants in the JUPITER trial, a randomized placebo-controlled primary prevention trial of statin therapy among individuals with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. Am. J. Cardiol. 100, 1659–1664
11 Kwak, B. et al. (2000) Statins as a newly recognized type of immunomodulator. Nat. Med. 6, 1399–1402
52 Alnog, Y. et al. (2004) Prior statin therapy is associated with a decreased rate of severe sepsis. Circulation 110, 880–885