

Statins: A review of benefits and risks.

Siobhra O'Sullivan, 4th Year Medicine

Clinical Points

- Statins have cholesterol and non-cholesterol (pleiotropic) effects
- Statins are central in the prevention of cardiovascular events associated with increased blood lipids and atherosclerotic lesions
- Recent and ongoing trials are investigating the benefits of early and intensive statin therapy versus current regimens, with promising results so far
- Cerivastatin was withdrawn in 2001 due to increased risk of rhabdomyolysis. Currently marketed statins have a superior safety profile, with the incidence of serious toxicities being extremely rare
- For at-risk patients, morbidity and mortality from cardiovascular events are greatly reduced with long-term statin use

INTRODUCTION

Since the groundbreaking Scandanavian Simvastatin Survival Study (4S) trial over a decade ago, the HMG-CoA reductase inhibitors, or Statins, have been central in the prevention of cardiovascular events associated with increased blood lipids and atherosclerotic lesions¹. With coronary heart disease being the number one cause of death in the US², statins are proven lifesaving medications. Most clinical trials of statins report a significant reduction in relative risk of coronary events versus placebo. Of note, three of the secondary-prevention, landmark, statin trials have reported a reduction in the relative risk for all-cause mortality: a 30% reduction in the Scandanavian Simvastatin Survival Study (4S)¹; a 22% reduction in the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID)³; and, a 13% reduction in the Heart Protection Study (HPS)⁴.

Concerns regarding the safety of the HMG-CoA reductase inhibitors peaked after the voluntary, worldwide withdrawal of cerivastatin (Baycol®, Lipobay®) in August 2001, due to a markedly increased rate of fatal rhabdomyolysis -nearly 80 times greater than that for other statins available at the time⁵. In 2006, the National Lipid Association of America (NLA) appointed a Statin Safety Task Force to address these issues and evaluate

statin safety. The NLA recently published its evaluation, finding statins to be generally well tolerated, having a high safety profile, with rare though potentially fatal side effects⁶.

This review article will focus on factors relating to lipids, inflammation and statin therapy, with an emphasis on the benefits and risks of this line of treatment. To put these in context, both the risk of drug side effects and benefits for cardiovascular disease are expressed in events per person years of statin treatment. It is important to keep in mind that atherogenesis is a multifactorial disease process, thus therapy should be directed toward all the modifiable risk factors.

BENEFITS

Effects on LDL, Endothelium and C-reactive Protein (CRP):

Statins are structural analogues of 3-hydroxy-3-methylglutaryl-coenzyme A, and competitively inhibit the HMG-CoA reductase enzyme responsible for the first committed step in sterol biosynthesis. By reducing intracellular levels of cholesterol, the expression of LDL receptors in liver cells is up-regulated, leading to increased clearance of LDL from the bloodstream. Thus, their main effect lies in the reduction of LDL cholesterol⁷.



Figure 1. Schematic representation of Statin effect on Cholesterol synthesis.

Statins also have numerous other effects, unrelated to lowering LDL, which are termed "pleiotropic" and include decreasing oxidative stress and vascular inflammation⁸ while increasing the stability of atherosclerotic lesions⁹. Almost all conventional risk factors for atherosclerosis are associated with endothelial dysfunction, which is characterized by damage due to reactive oxygen species which promote the release of transcription factors, growth factors, pro-inflammatory cytokines, chemokines and adhesion molecules¹⁰. In patients with coronary artery disease and hyperlipidaemia, statins improve endothelial function, decrease the plasma concentrations of tumor necrosis factor- α (TNF- α), and reduce morbidity and mortality¹¹. Other cholesterol-independent effects of statins include the inhibition of platelet function by decreasing the production of thromboxane A₂ and decreasing the cholesterol content of platelet membranes, thus lowering their thrombogenic potential¹².

Statins are also known to reduce C-reactive protein (CRP) levels and a variety of experimental observations suggest a direct role for CRP in the pathogenesis of atherosclerosis. Specifically, CRP renders oxidized LDL more susceptible to uptake by macrophages, induces the expression of vascular-cell adhesion molecules, stimulates the production of tissue factor, and impairs the production of nitric oxide^{13,14,15}. Ridker and Cannon concluded that patients with a low CRP level, after statin treatment, had better clinical outcomes than those with higher levels, regardless of the resultant level of LDL-cholesterol¹⁶.

Clinical Benefits

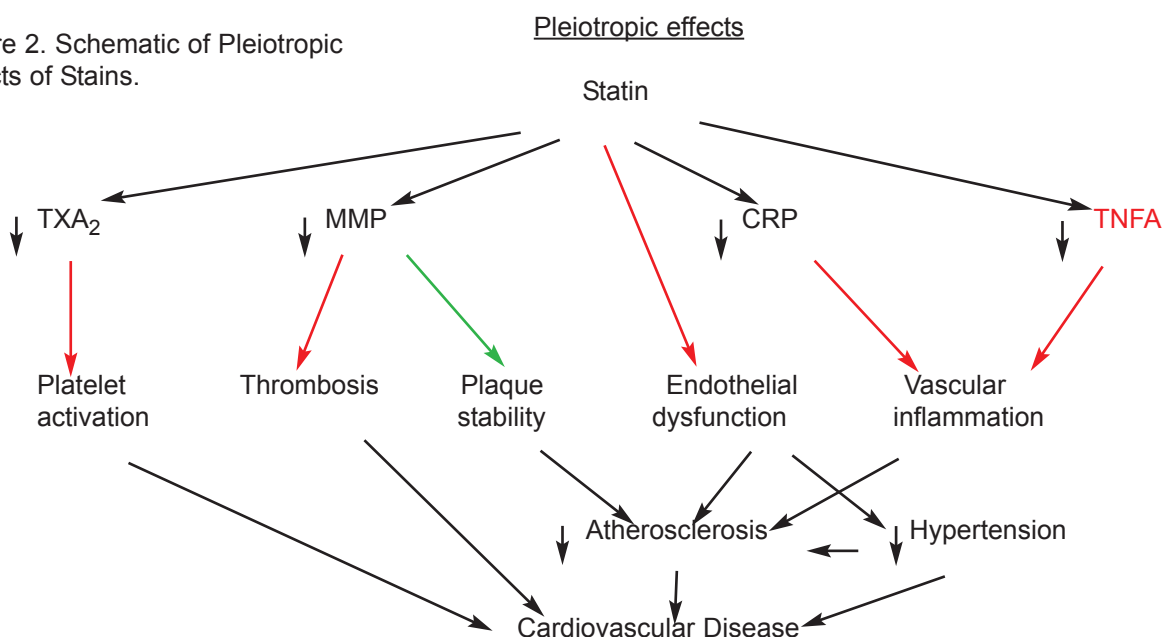
Recent trials have demonstrated better clinical outcomes with intensive rather than moderate statin treatment. The

Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial¹⁷ demonstrated improved outcomes, with hospitalisation rates for heart failure significantly reduced after an acute coronary syndrome (1.6% with intensive therapy vs. 3.1% with moderate treatment). The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial¹⁸ demonstrated reduced rates of progression of atherosclerosis after intensive (80mg atorvastatin) treatment when compared with moderate (40mg pravastatin) treatment.

Vigorous statin therapy can lead to a reduction in acute coronary events within 2-6 months. This is thought to be due to the mitigation of the inflammatory activity of macrophages, not the reduction in cholesterol. Intensive statin treatment produces greater reductions in both LDL-C and inflammatory markers such as CRP and interleukin-6 (IL-6), suggesting a relationship between these markers and disease progression¹⁹. Whether this anti-inflammatory action of statins is a direct effect, or mediated through reduction of LDL-C, is not yet fully understood but studies have shown that on sudden cessation of statins, CRP levels respond independent of LDL levels²⁰.

Vigorous therapy can also cause slow, minimal regression of plaques^{21,22} and one study has reported a 6.3% reduction in atheroma thickness at 12 months²³. Furthermore, stabilisation of atherosclerotic plaques occurs via the inhibition of matrix metalloproteinases (MMPs) release by activated macrophages within the lesion. This prevents the breakdown of the collagen in the fibrous cap, reducing the risk of plaque rupture, thrombosis, and the development of acute coronary syndrome¹².

Figure 2. Schematic of Pleiotropic Effects of Statins.



RISKS

Adverse Effects

Statins are responsible for a wide range of adverse effects, ranging from mild gastro-intestinal disturbances to life-threatening conditions such as rhabdomyolysis. When considering the risk-benefit profile of statin therapy, it is best to discuss side effects in terms of events per person year of treatment, as described by the NLA. Based on the data available, excluding Cerivastatin, current statins on the market have a very good safety profile and a proven reduction in mortality due to cardiovascular disease²⁴. What follows is a summary of the major adverse effects reported.

Effects on Muscle

Among the most reported adverse effects of statins are nausea, diarrhea, constipation, and those relating to myotoxicity, ranging from mild myalgia to the rare instance of rhabdomyolysis. Clinical signs of rhabdomyolysis include severe muscle pain and tenderness on palpation, muscle weakness, and dark colored urine due to myoglobinuria. Rhabdomyolysis is associated with profoundly elevated creatinine kinase levels and acute renal failure secondary to myoglobinuria. Fatal rhabdomyolysis is the only substantial, well-defined cause of mortality associated with statin therapy. The estimated risk of developing rhabdomyolysis is 0.3 per 100,000 person years, with a fatality rate of 9%²⁵. Combining any statin with a fibrate increases the risks for rhabdomyolysis to almost 6.0 per 100,000 person years²⁶. On the other hand, survival benefit has a rate of 360 per 100,000 person years due solely to reduction in cardiovascular mortality²⁷.

The incidence of myotoxicity increases with the dose and concentration of statins, although the specific mechanism is unknown²⁸. This finding highlights the importance of CYP450 drug interactions. Lovastatin, simvastatin and atorvastatin are metabolised by the CYP3A4 isozyme while rosuvastatin and fluvastatin are metabolised by CYP2C9. Thus, it follows that drugs which inhibit these enzymes (eg. verapamil, azole antifungals, macrolides, diltiazem and grapefruit juice) serve to decrease the metabolism of their substrates, leading to an increased risk of toxicity. Pravastatin pharmacokinetics, on the other hand, tends not to be influenced by administration of CYP inhibitors as it is not subject to CYP metabolism^{29,30}.

Effects on the Liver

Elevations in liver enzymes, specifically AST and ALT, to greater than three times the upper normal limit, are a dose-related effect of statins occurring in less than 1% of patients receiving initial treatment, and in 1-3% of those on higher doses (eg. 80mg atorvastatin)³¹. This effect is

typically asymptomatic and transient, resolving spontaneously in the majority of cases even with continued therapy³². Furthermore, the epidemiological data on liver dysfunction and acute liver failure do not establish causality. The rate at which liver failure occurs in statin-treated patients is estimated at 0.5 -1 per 100,000 person years of treatment, which is equal to the background rate of liver failure in the general population³³. This suggests either no relationship between statin therapy and liver failure, or that idiosyncratic reactions occur in some patients.

Current prescribing recommendations suggest liver function tests (LFTs) be performed at baseline and at 6-12 weeks after initiation of treatment, or when an increased dose is commenced. There is no evidence to suggest routine monitoring of LFTs in patients receiving statins, nor is it suggested that patients withdraw from therapy for an isolated transaminase level of 1-3 times the upper limit of normal (ULN), instead the test should be repeated and other aetiologies ruled out³¹. Patients should be warned of symptoms indicative of hepatotoxicity, such as jaundice, malaise and fatigue.

Effects on the Kidney

Current literature provides no evidence that statins cause acute or chronic renal damage. Of note, the NLA statin safety task force found that "in the absence of infrequent rhabdomyolysis, there is no evidence that the HMG Co-A reductase inhibitors cause renal failure or insufficiency"³⁴. Results from the Prospective Pravastatin Pooling Project³⁵, which included results from 3 randomised clinical trials of pravastatin [1-Cholesterol and Recurrent Events (CARE)³⁶, 2-LIPID Trial 3, and 3-West of Scotland Coronary Prevention Study (WOSCOPS)³⁷] found that renal disease and failure occurred more frequently in placebo controls than in pravastatin-treated patients, with rates of 0.8% and 0.5% respectively. In addition, several studies suggest a potential protective effect of long-term statin treatment. A 2001 meta-analysis, involving 13 trials which studied the renal effects of lipid lowering medications, including statins, concluded that treated patients had decreased proteinuria and a lower rate of decline in glomerular filtration rate compared with controls³⁸. As with hepatic function, current practice is to obtain a baseline assessment of renal function.

Effects on the Nervous System

Statins are highly lipophilic and thus have greater potential to cross the blood-brain barrier and affect the central nervous system. However, the balance between diffusion in and out of the CNS by transporters determines the actual exposure of the brain to statins. No effects of the lipophilic properties of statins have been shown with regards to efficacy and safety³⁹. Law and Rudnicka estimate peripheral neuropathy caused by statins to have an incidence of 12 per 100,000 person

years²⁵. Conversely, neurological data suggest that statins may have a beneficial effect on CNS disorders, including Alzheimer's disease and other dementias⁴⁰. The NLA has determined the risk of peripheral neuropathy to be very small and recommends that if peripheral neuropathy develops, other aetiologies should first be ruled out. If no other cause is found, the statin should be withheld for 1-3 months. If, on cessation of treatment, symptoms improve, a presumptive diagnosis of statin-attributable neuropathy can be made. However, it is recommended that another statin and dose be considered because of the known benefits of therapy⁶.

CONCLUSION:

Concerns over the safety of statins have increased since the voluntary withdrawal of Cervistatin from the world market, in 2001. Statins have been linked to adverse effects involving the liver, kidney, and nervous system. Nevertheless, it is important to note that in the absence of rhabdomyolysis, statins do not cause renal insufficiency. Baseline levels of liver transaminases and renal function tests are recommended before initiating treatment. It is also appropriate to measure transaminase levels periodically. Elevated LFTs represent a dose-related effect which may resolve spontaneously or with dose/drug change. Serious muscle toxicities with statins are extremely rare and given the magnitude of cardiovascular events avoided due to long-term statin therapy the benefits of these drugs most certainly outweigh the risks. As with all medications, patients and physicians should be aware of potential adverse effects and are encouraged to report all events.

REFERENCES

- Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-1389
- Thom T et al. Heart Disease and Stroke Statistics-2006 Update. A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2006;113:e85-e151
- The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349-1357
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study (HPS) of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22
- Staffa et al. Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med*. 2002;346:539-540
- McKenny JM, Guyton JR et al. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol*. 2006;97:89C-94C
- Katzung BG. *Basic and Clinical Pharmacology*. Lange 2004. 9th Ed.
- Grines CL. The role of statins in reversing atherosclerosis. What the latest regression studies show. *J Int Cardiol* 2006;19:3-9
- NgDS. The role of statins in oxidative stress and cardiovascular disease. *Curr Drug Targets Cardiovasc Haematol Disord* 2005;5(2):165-175
- Cohn JN et al. Surrogate markers for cardiovascular disease: functional markers. *Circulation* 2004;109(25 suppl 1):V31-46.
- Leite-Moreira AF, Castro-Chaves P. Heart failure: statins for all? *Heart* 2006;92:1537-1538
- Takemoto M, Liao JK. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Arterioscler Thromb Vasc Biol* 2001;21:1712-1719.
- Torzewski M et al. C-reactive Protein in the Arterial Intima: role of C-reactive protein receptor-dependent monocyte recruitment in atherogenesis. *Atheroscler Thromb Vasc Biol* 2000;20:2094-2099.
- Cermak J et al. C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. *Blood* 1993;82:513-520.
- Verma S et al. A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. *Circulation* 2002;106:913-919.
- Ridker PM, Cannon CP. CRP levels and outcomes after statin therapy. *N Engl J Med* 2005;352:20-28.
- Cannon CP et al. Design of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)-TIMI22 trial. *Am J Cardiol* 2002;89:860-861
- Nissen SE et al. Effect of Intensive Compared with Moderate Lipid-Lowering Therapy on Progression of Coronary Atherosclerosis (REVERSAL). A randomised control trial. *JAMA* 2004;291:1071-1080.
- Nissen SE et al. Statin Therapy, LDL Cholesterol, C-Reactive Protein, and Coronary Artery Disease. *N Engl J Med* 2005;352:29-38.
- Li JJ, Li YS et al. Changes of plasma inflammatory markers after withdrawal of statin therapy in patients with hyperlipidemia. *Clin Chim Acta* 2006;366(1-2):269-273
- Acevedo M, Sprecher DL et al. Routine treatment after acute coronary syndromes? *Am Heart J* 2002;143:940-942
- Takemoto M, Liao JK. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors 2001;21:1712-1717
- Jensen LO, Thayssen P et al. Regression of coronary artery atherosclerosis by simvastatin: a serial intravascular ultrasound study. *Circulation* 2004;110:265-270.
- Wilt TJ et al. Effectiveness of statin therapy in adults with coronary heart disease. *Arch Intern Med* 2004;164:1427-1436
- Law M, Rudnicka AR. Statin Safety: a systematic review 2006;97[suppl]52C-60C
- Graham DJ, Staffa JA et al. Incidence of hospitalised rhabdomyolysis in patients treated with lipid lowering drugs. *JAMA* 2004;292:2585-2590
- Guyton JR. Benefit versus Risk in Statin Treatment. *Am J Cardiol* 2006;97[suppl]:95C-97C.
- Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother*. 2001;35:1096-1107.
- Bottomoff MB. Statin safety and drug interactions: clinical implications. *Am J Cardiol* 2006 17;97(8A):27C-31C.
- Igel M, Sudhop T, von Bergmann K. Metabolism and drug interactions of 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors (statins). *Eur J Clin Pharmacol* 2001;57(5):357-364.
- US Food and Drug Administration, Center for Drug

Evaluation and Research. Statins and hepatotoxicity. [US Food and Drug Administration website]: http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3622b2b_safety_review.pdf

32. Coden DE, Anania FA. An assessment of statin safety by hepatologists. *Am J Cardiol* 2006;97[suppl]:77C-81C

33. Tolman KG. The liver and lovastatin. *Am J Cardiol* 2002;89:1374-1380.

34. Kasiske BL, Wanner C, O'Neill WC. An assessment of statin safety by nephrologists. *Am J Cardiol*. 2006;97[suppl]:82C-85C.

35. Pfeffer MA, Keeck A, Sachs FM et al. Safety and tolerability of pravastatin in long-term clinical trials: Prospective Pravastatin Pooling (PPP) project. *Circulation* 2002;105:2341-2346

36. Tonelli M, Moyé L et al, for the Cholesterol and Recurrent

Events (CARE) trial Investigators. Effect of pravastatin on loss of renal function in people with moderate chronic renal insufficiency and cardiovascular disease. *Am Soc Nephrol*. 2003;14:1605-1613.

37. Sheppard J, Cobbe SM et al, for the West of Scotland Coronary Prevention Study Group. Prevention of coronary artery disease in men with hypercholesterolaemia. *N Engl J Med*. 1995;333:1301-1307.

38. Fried LF, Orchard TJ, Kasiske BL, for the Lipids and Renal Disease Progression Meta-Analysis Study Group. Effect of lipid reduction on the progression of renal disease: a meta-analysis. *Kidney Int*. 2001;59:260-269.

39. Bays H. Statin safety: an overview and assessment of the data-2005. *Am J Cardiol*. 2006;97[suppl]:6C-26C.

40. Brass LM, Alberts MJ, Sparks L. An assessment of statin safety by neurologists. *Am J Cardiol* 2006;97[suppl]:86C-88