Statins: A review of benefits and risks.

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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- Cerivastatin was withdrawn in 2001 due to increased risk of rhabdomyolysis.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 lesions[1]. With coronary heart disease being the number one cause of death in the US[2], 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 time[5]. 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 effects[6].

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 commited 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 cholesterol[7].

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 inflammation[8] while increasing the stability of atherosclerotic lesions[9]. 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 molecules[10]. 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 mortality[11]. Other cholesterol-independent effects of statins include the inhibition of platelet function by decreasing the production of thromboxane A_2 and decreasing the cholesterol content of platelet membranes, thus lowering their thrombogenic potential[12].

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-cholesterol[16].

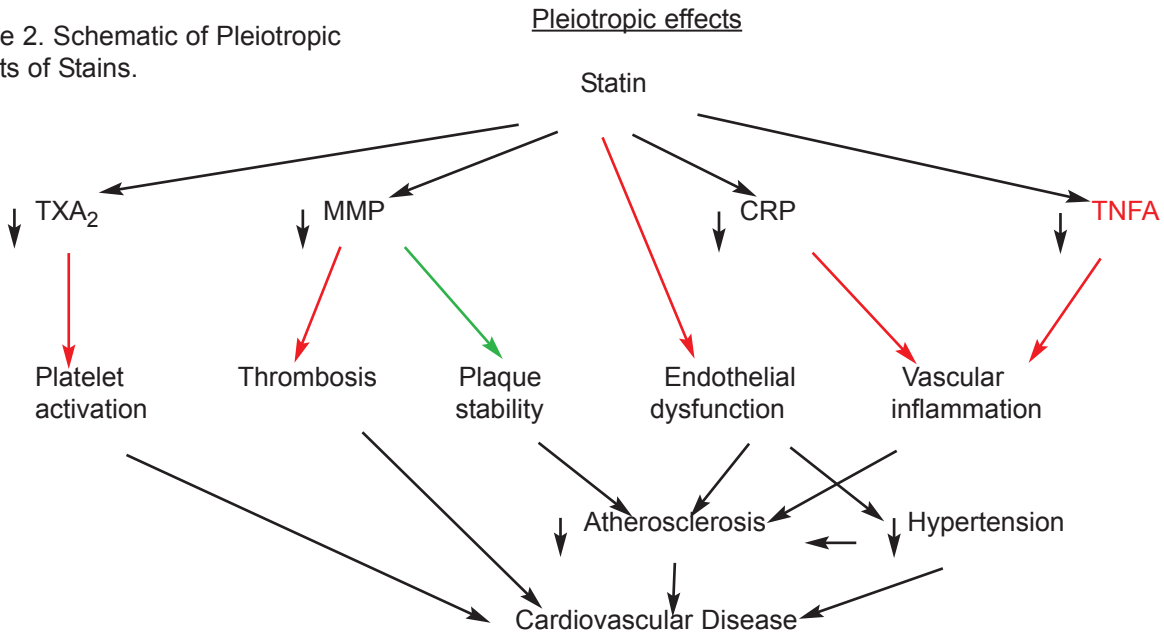
Clinical Benefits

Recent trials have demonstrated better clinical outcomes with intensive rather than moderate statin treatment. The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial[17] 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) trial[18] 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 progression[19]. 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 levels[20].

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 months[23]. 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 syndrome[12].

Figure 2. Schematic of Pleiotropic Effects of Stains.



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 disease[24]. 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 years[26]. On the other hand, survival benefit has a rate of 360 per 100,000 person years due solely to reduction in cardiovascular mortality[27].

The incidence of myotoxicity increases with the dose and concentration of statins, although the specific mechanism is unknown[28]. 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 therapy[32]. 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 population[33]. 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 out[31]. Patients should be warned of symptoms indicative of hepatotoxity, 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 rhrabdomyolysis, there is no evidence that the HMG Co-A reductase inhibitors cause renal failure or insufficiency"[34]. Results from the Prospective Pravastatin Pooling Project[35], which included results from 3 randomised clinical trials of pravastatin [1-Cholesterol and Recurent 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 controls[38]. 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 safety[39]. Law and Rudnicka estimate peripheral neuropathy caused by statins to have an incidence of 12 per 100,000 person

years[25]. Conversely, neurological data suggest that statins may have a beneficial effect on CNS disorders, including Alzheimer's disease and other dementias[40]. 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 therapy[6].

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 insuffiency. 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.

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