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Review Article

Statins and stroke

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ABSTRACT

Stroke is a heterogeneous condition with a number of possible etiologies. Patients with different underlying stroke pathophysiologies may variably respond to specific preventive treatment strategies. Statin outcome trials in subjects with established coronary artery disease, hypertension, diabetes, or at high vascular risk have shown a consistent 17–21% relative reduction in the risk of incident stroke. The benefits observed with statins appear to be greater than what might be expected from changes in lipid levels alone, because of the additional pleiotropic effects.

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Stroke is a heterogeneous condition with a number of possible etiologies.¹ While myocardial infarction (MI) is almost always attributable to atherothrombotic disease, brain infarction stems from a host of conditions (e.g., rheumatic heart disease, arterial dissection, elastic tissue disease, intracranial small vessel disease, atherosclerotic carotid stenosis, etc.). Stroke subtyping systems, such as the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, help classify patients into the most likely cause category.² Patients with different underlying stroke pathophysiologies may variably respond to specific preventive treatment strategies. For example, atherothrombotic stroke is best prevented by antiplatelet agents, whereas cardioembolic stroke attributable to atrial fibrillation is best prevented by vitamin K antagonists.³ Statin outcome trials in subjects with established coronary artery disease,

hypertension, diabetes, or at high vascular risk have shown a consistent 17–21% relative reduction in the risk of incident stroke.⁴

Statins are potent inhibitors of cholesterol biosynthesis. In clinical trials, statins are beneficial in the primary and secondary prevention of coronary heart disease. However, the overall benefits observed with statins appear to be greater than what might be expected from changes in lipid levels alone, suggesting effects beyond cholesterol lowering. Indeed, recent studies indicate that some of the cholesterol-independent or “pleiotropic” effects of statins involve improving endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation, and inhibiting the thrombogenic response. Furthermore, statins have beneficial extrahepatic effects on the immune system,

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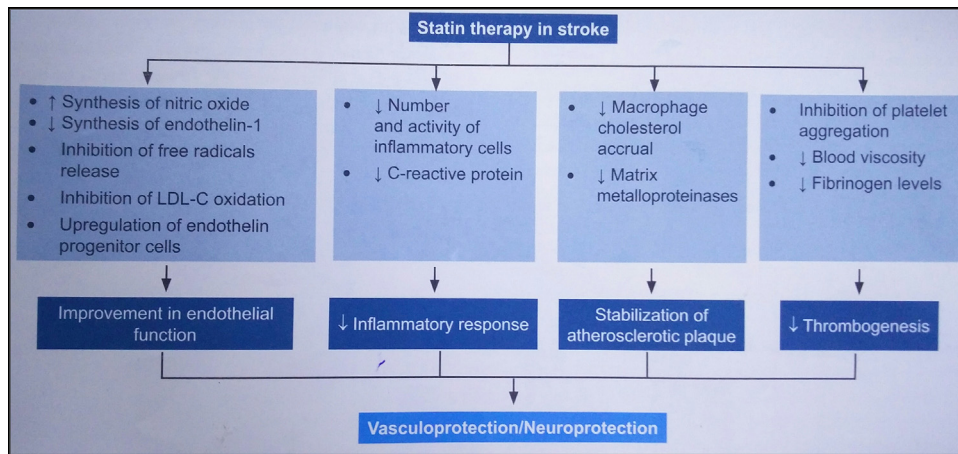


Fig. 1 – Pleiotropic effects of statins.

CNS, and bone. Many of these pleiotropic effects are mediated by inhibition of isoprenoids, which serve as lipid attachments for intracellular signaling molecules. In particular, inhibition of small GTP-binding proteins, Rho, Ras, and Rac, whose proper membrane localization and function are dependent on isoprenylation, may play an important role in mediating the pleiotropic effects of statins.⁵

Statins exert many pleiotropic effects in addition to the lowering of serum cholesterol levels. These additional properties include beneficial effects on endothelial function and blood flow, decreasing LDL-C oxidation, enhancing the stability of atherosclerotic plaques, inhibiting vascular smooth muscle proliferation and platelet aggregation, and reducing vascular inflammation (Fig. 1). Recent evidence suggest that most of these effects are mediated by statin's inhibitory effect on isoprenoid synthesis. In particular, inhibition of Rho GTPases in vascular wall cells by statins leads to increased expression of atheroprotective genes and inhibition of vascular SMC proliferation.⁵

Although MI is closely associated with serum cholesterol levels, neither the Framingham Heart Study nor the Multiple Risk Factor Intervention Trial demonstrated significant correlation between ischemic stroke and serum cholesterol levels.^{6,7} An intriguing result of large clinical trials with statins is the reduction in ischemic stroke.⁸ For example, the recent Heart Protection Study shows a 28% reduction in ischemic strokes in over 20,000 people with cerebrovascular disease or other high-risk conditions.⁹ The proportional reductions in stroke were approximately one-quarter in all subcategories studied, including those aged over 70 years at entry and those presenting with different levels of blood pressure or lipids, even when the pretreatment LDL-C was below 3.0 mmol/L (116 mg/dL). Thus, the findings of these large statin trials raise the interesting question of how a class of cholesterol-lowering agents can reduce ischemic stroke when ischemic stroke is not related to cholesterol levels. It appears likely that there are cholesterol-independent effects of statins, which are beneficial for ischemic stroke. Some of these beneficial effects may relate to the effects of statins on endothelial and platelet function.⁵

A large population-based prospective study, which evaluated the impact of statin treatment during acute phase of ischemic stroke, studied 12,781 patients with acute ischemic stroke, 59% of who received statin therapy. In-hospital mortality and morbidity at 3 months after discharge were noted to be significantly lower in statin group compared to controls (Fig. 2). Similarly, disability rates in the survivors at the time of discharge and 3 months after discharge were lower in statin group patients compared with controls (Fig. 3).¹⁰

Similar findings were reverberated in one of the major statin trial – Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial by Stroke Subtypes. In SPARCL trial, subjects with stroke or TIA without known coronary heart disease were randomized to atorvastatin 80 mg/d or placebo. The SPARCL primary endpoint was fatal or nonfatal stroke. Secondary endpoints included major cardiovascular events (MCVE; stroke plus major coronary events). Particular emphasis was on the outcome for different stroke subtypes.

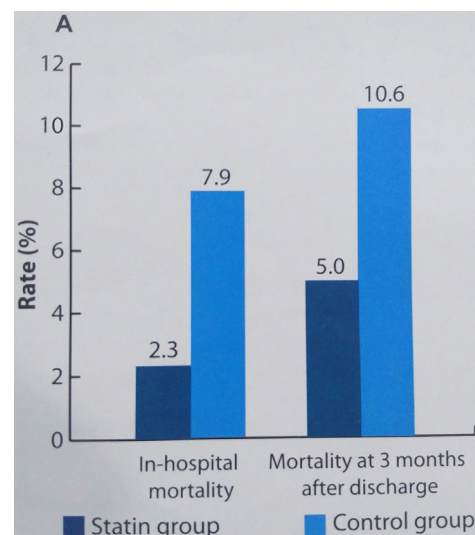


Fig. 2 – The impact of statin treatment on death in patients with acute ischemic stroke.

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