Role of Statins in the Treatment and Prevention of Stroke

Introduction

Epidemiological studies suggest that hyperlipidemia is not a major risk factor for stroke, yet 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) decrease the risk of stroke in patients with vascular disease or at high risk of vascular disease.\(^1\)\(^-\)\(^6\) Moreover, the benefit of statins appears to be independent of baseline cholesterol; persons with normal cholesterol experience a similar degree of risk reduction as patients with elevated cholesterol.\(^3\) Results of dedicated stroke trials to determine the benefit of statins in secondary stroke prevention are not yet available, although the Heart Protection Study did include a large population of patients with cerebrovascular disease and stroke.\(^3\) Interestingly, among patients with a history of stroke, statins did not decrease the risk of recurrent stroke, but did decrease the risk of myocardial infarction.\(^7\)

While epidemiological studies fail to show a dramatic effect of hyperlipidemia on ischemic stroke risk, low cholesterol levels are associated with an increased risk of intracerebral hemorrhage (ICH).\(^8\)\(^,\)\(^9\) Importantly, statin therapy has not been associated with an increased risk of ICH in any of the studies done to date.\(^4\)\(^,\)\(^5\)\(^,\)\(^7\) Furthermore, statin use may be associated with lessened stroke severity in patients with ischemic stroke, and animal data points to a similar benefit in ICH.\(^10\)\(^,\)\(^11\) These observations, along with the disconnect between the epidemiologic data regarding the role of cholesterol in stroke risk and the benefit of statins in stroke prevention suggest that the benefits of statins may be related to nonlipid effects of the drugs. Indeed, statins affect multiple biological systems, including the immune system. Prevention of vascular outcomes in trials of statins is strongly linked to a decrease in C-reactive protein.\(^12\)\(^-\)\(^13\) These potent antiinflammatory effects also appear to translate into benefit in the treatment of multiple sclerosis and rheumatoid arthritis.\(^14\)\(^,\)\(^15\)

Statins have both neuroprotective as well as neurorestorative effects in the treatment of experimental stroke and neural injury. Statins improve endothelial function and have anticoagulant, antiinflammatory, and antithrombogenic properties, all of which may foster neuroprotective effects.\(^16\)\(^,\)\(^17\) These therapeutic properties are independent of lipid lowering.\(^18\)\(^,\)\(^19\) Pretreatment of experimental stroke with simvastatin significantly reduces the volume of cerebral infarction.\(^20\) Treatment with simvastatin after stroke onset likewise has neuroprotective effects.\(^21\)\(^,\)\(^22\) The antiinflammatory effects of statins suggest that these agents may also be effective when used in combination with thrombolytic therapies, such as with recombinant tissue plasminogen activator, possibly extending the therapeutic window and reducing hemorrhagic transformation. The multiple therapeutic pathways activated by statins also include those associated with restorative therapies. Statins administered to animals 24 hours after stroke increase expression of neurotrophic factors such as vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF), amplify endogenous brain plasticity, and reduce neurological deficits.\(^23\)

Statins are widely used to reduce cholesterol levels and have a well characterized and generally good safety profile. The pleiotropic effects of these agents in enhancing endothelial NO synthase, reducing vascular inflammation, promoting tissue perfusion, and in amplifying brain plasticity suggest that statins should be investigated as prophylactic, acute neuroprotective and delayed neurorestorative treatment for stroke.

The articles in this section explore some of the nonlipid effects of statins as they pertain to the treatment and prevention of stroke.

References


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