Editorial

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The current status of statins in stroke prevention

Abstract

Statins or 3-hydroxl- 3-methyl glutaryl coenzyme A reductase inhibitors are drugs that are primarily used to treat dyslipidemia. Statins are recommended for use in ischemic stroke related to small and large vessel disease, although studies suggest that their use in primary prevention and in other subtypes of stroke may also be beneficial. The benefits of statins in stroke prevention and improvement of neurologic outcome after acute ischemic stroke are related to their pleiotropic effects. These include expression of endothelial Nitric Oxide Synthase (eNOS), angiogenesis, anti -inflammatory action, stabilization of the endothelial layer and enhancement of tissue plasminogen activator. Numerous randomized controlled trials, meta-analyses and population based studies have highlighted the importance of statins in prevention of stroke and improvement of neurologic outcome. Many concerns have been raised regarding their adverse effects such as myopathy, elevated transaminases and increased risk of intracranial hemorrhage and cancer. However, studies have shown that statins can be used over a long period of time without any significant adverse events. Current stroke prevention guidelines recommend the initiation of statins in patients with evidence of atherosclerosis and an LDL cholesterol level >100mg/dL without known coronary heart disease, and also in patients with elevated cholesterol or comorbid coronary heart disease.

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Abbreviations: eNOS, endothelial nitric oxide synthase; CARE, cholesterol and recurrent events study; LIPID, long-term intervention with pravastatin in ischemic disease; JUPITER, justification for the use of statins in prevention, an intervention trial evaluating rosuvastatin; s-CRP, sensitive C reactive protein; SPARCL, stroke prevention by aggressive reduction in cholesterol levels; J-STARS, Japan statin treatment against recurrent stroke; RAPID-TIA, rapid primary care initiation of drug treatment for transient ischaemic attack; AIS, acute ischemic stroke; ThraST, THRombolysis and Statins

Introduction

Statins or 3-hydroxl- 3-methyl glutaryl coenzyme A reductase inhibitors are drugs that are primarily used to treat dyslipidemia [1]. They are beneficial in primary and secondary prevention of stroke [2]. Statins are recommended for use in ischemic stroke related to small and large vessel disease, although studies suggest that their use in primary prevention and in other subtypes of stroke may also be beneficial [1,3,4] The benefits of statins are related to their pleiotropic effects and to their lipid lowering properties. However, the predominant effect in hyperacute stroke is probably pleotropic rather than lipid lowering [1,2] Blanco et al. [5] found that withdrawal of statins in hyperacute stroke, even for 72 hours was related with a significantly worse outcome. This effect was independent of the LDL-C levels. The major pleiotropic effect of statins is the expression of endothelial Nitric Oxide Synthase (eNOS) which causes vasodilation and enhancement of cerebral blood flow. This, in addition to enhancement of collateral circulation and cerebrovascular reactivity, helps improve the infarct volume [6,7] Other pleiotropic effects include angiogenesis, anti -inflammatory action, stabilization of the endothelial layer and enhancement of tissue plasminogen activator [1,2] all of which can contribute to improvement of cerebral blood flow and to the reduction of the infarct volume.

Benefits of statin use in stroke prevention

Prevention of first ever strokes and recurrent strokes

A summary of the major randomized controlled trials and meta-analyses studying the role of statins in prevention of stroke has been provided in Table 1. The CARE (Cholesterol and Recurrent Events study)[8] and the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease)[9] trials recruited patients with MI, and with MI and unstable angina, respectively. In the former study, the investigators found a risk reduction of 32% (95% CI: 4-52 %; p=0.03) in all cause stroke in the statin group. In the latter study, there was a 23% risk reduction (95% CI: 5-38%, p=0.02) in ischemic stroke in the statin group. In the Heart Protection Study[10] 20,536 adults aged between 40-80 years who were suffering from diabetes, coronary heart disease or other occlusive arterial disease were randomized to receive either simvastatin or placebo. There was significant reduction in the incidence of fatal and non- fatal stroke (4.3% vs. 5.7%, p<0.001). Overall, the treatment group had a highly significant reduction in the incidence of first stroke, which was attributed to the reduction in ischemic strokes (2.8% vs. 4%, p<0.001), since there was no difference found in the incidence of hemorrhagic strokes (0.5% vs 0.5%, p=0.8). A systematic review of eighteen randomized controlled trials[11] encompassing 114,081 subjects, showed that statins reduced the overall incidence of stroke as compared to placebo (odds ratio: 0.80; 95% CI: 0.74-0.87; p<0.00001) in high risk individuals. The benefits of statins on major cardiovascular events in the elderly were confirmed by a meta-analysis [3] including eight randomized controlled trials which encompassed 24,674 subjects. The study found that compared to placebo, statins significantly reduced the risk of stroke by 23.8 % ((RR: 0.762 (95% CI: 0.626 to 0.926); p =0.006)). The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial[12] evaluated the effect

of statins in reducing vascular events in healthy adults with a normal cholesterol level <130mg/dL and elevated sensitive C reactive protein (s-CRP). The study was terminated early when the benefits of the treatment arm were realized to be highly significant for the treatment arm in reducing stroke, MI and the need for revascularization.

The SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial[13] studied the role of secondary prevention with statins in stroke. Over a mean follow up period of 4.9 years, the treatment group had significantly lower number of ischemic stroke events, with a Hazard Ratio of 0.79 (95% CI: 0.66-0.95).

There are two ongoing randomized controlled trials which aim to study the effect of statins in secondary prevention of stroke. The J-STARS (Japan Statin Treatment Against Recurrent stroke)[14] is a multicenter, randomized controlled study of patients with non- cardio-embolic ischemic stroke which aims to examine the role of statins in the secondary prevention of stroke in the Japanese patients .The follow evaluations are due to end in 2014 and the results are awaited. The RAPID-TIA (RApid Primary care Initiation of Drug treatment for Transient Ischaemic Attack)[15] is a pilot randomized controlled trial which aims to address the benefits of early initiation of statins in addition to aspirin by primary care and emergency physicians in patients with suspected TIA or minor stroke at the time of referral to a specialist. Both these studies will help broaden our understanding about the use of statins in secondary prevention.

Table 1 Major RCTs and Meta-Analyses studying the role of statins in stroke prevention

Study	Type of Study	Sample Size	Inclusion Criteria	Statin Used	Significant Finding*
Plehn et al.[8]	RCT	4159	MI	Pravastatin 40 mg/day	31% RRR for all-cause stroke
White et al.[9]	RCT	9014	MI,UA	Pravastatin 40 mg/day	23% RRR for ischemic stroke
Heart Protection Study[10]	RCT	20,536	CHD, DM, Stroke, Other vascular diseases	Simvastatin 40mg/day	25% RRR first ischemic strokes
Goldstein et al.[13]	RCT	4731	Stroke, TIA without CHD	Atorvastatin 80mg/day	HR for incidence of ischemic stroke : 0.79
Ridker et al.[12]	RCT	17,802	Elevated s-CRP with normal cholesterol	Rosuvastatin 20mg/day	HR 0.52 for incidence of any stroke
Wang&Zhang[11]	Meta-Analysis	114,081	DM, CHD, hypertension, hypercholesterolemia, MI	Multiple	OR 0.80 for incidence of stroke
Savarese et al.[3]	Meta-Analysis	24,674	Elderly (>=65 y) without established cardiovascular disease	Multiple	RRR 24% for risk of stroke

*Results were considered as significant at p<0.05

RCT, randomized controlled trial; MI, myocardial infarction; UA, unstable angina; CHD, coronary heart disease; TIA, transient ischemic attack; s-CRP, sensitive c-reactive protein; DM, diabetes mellitus; HR, hazard ratio

This trial is of significance for two reasons,

    i.   It provided evidence that initiating statin therapy in patients without elevated cholesterol reduced the risk of stroke significantly and

    ii.   The study proved that s-CRP was not just an inflammatory marker, but was associated with all vascular events including stroke.

Improvement of neurological outcomes after acute ischemic stroke

Statins, when initiated after an acute ischemic stroke (AIS), improve the neurological outcome and survival. In a retrospective study,[16] we found that patients treated with statins after the onset of AIS had a significantly higher probability of a favorable outcome at 12 weeks defined as NIHSS (National Institute of Health Stroke Scale Score ≤2(OR 1.92, CI:1.27-2.91, p=0.002) and the modified Rankin Scale score ≤2(OR 1.57, CI: 1.04-2.38; p=0.03). A meta- analysis of 27 studies[7] encompassing 113, 148 patients found that initiating statin treatment at stroke onset was associated with reduced likelihood of all cause death at 30 days (Pooled OR 0.63; 95 CI: 0.54-0.74; p<0.001), 90 days (pooled OR, 0.71; 95% CI: 0.62-0.82; p<0.001) and at 1 year (pooled OR 0.80; 95% CI: 0.67-0.95; p=0.01). This has been reiterated by numerous population and hospital based studies which have shown significant reduction in in- hospital mortality rates as well as mortality rates 3months after stroke onset.[17,18] An evaluation of the Registry for Canadian stroke network[19] found that in-hospital discontinuation of statin was associated with higher mortality (Odds ratio 2.0; 95% CI: 1.30-3.04). The ThraST (THRombolysis and Statins)[20] study found that initiating statins in AIS in patients treated with intravenous thrombolysis was associated with significant neurologic improvement (p<0.001), favorable functional outcome (p=0.003) and reduced risk of neurological deterioration (p<0.001).

The SPARCL trial provided evidence for the use of high dose statins to prevent recurrent ischemic stroke and a suggestion of improved stroke outcome. This was re- iterated by the North Dublin Population Cohort Study[21] which showed a reduction in the mortality for each change in dose category at 7days (OR, 0.18; CI, 0.62-0.49; P=0.001), 3 months (OR, 0.36; CI, 0.21-0.63; P<0.001) and 1year (OR, 0.59; CI, 0.40-0.89; P=0.01) when statins were administered after stroke onset. This has been attributed to the dose dependent nature of the pleiotropic effects of statins, especially the enhancement of eNOS and antithrombotic effects.[22]

Are concerns regarding adverse effects overstated?

A few concerns have been raised regarding the use of statins. These include muscle symptoms such as myositis, myalgias and

rhabdomyolysis; elevation of liver transaminases and an increased risk of intracranial hemorrhage and cancer. Prior studies have shown that statins at high doses are well tolerated with minimum myotoxicity and hepatotoxicity.[22–24] Two large systematic reviews, one comprising 23 randomized and 19 observational studies and the other comprising 31 randomized controlled trials[25] found no significant increase in the incidence of intracranial hemorrhage in patients treated with statins. The 11–year follow up of morbidity and mortality in the Heart Protection Study population[26] concluded that the long term use of statins did not have any adverse effect on particular non-vascular causes of mortality or major morbidity (including site specific cancers). Also, the study did not find any relationship between long term statin use and intracranial hemorrhage.

Conclusion

Statins are advocated for use in preventing recurrent stroke and improving neurological outcome after AIS. Studies have shown the retention of the benefits with long term use of statins[26,27] without any major adverse events. Statins can also be used in preventing first ever ischemic strokes in high risk individuals. Current stroke prevention guidelines recommend the initiation of statins in patients with evidence of atherosclerosis and an LDL cholesterol level >100mg/dL without known coronary heart disease and also in patients with elevated cholesterol or comorbid coronary heart disease.[2] Generating more data regarding the effect of statin dose on stroke prevention by conducting randomized controlled trials which evaluate the effects of low-dose vs. high dose statins will help augment the role of statins in primary and secondary prevention of stroke.

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None.

Conflicts of interest

The authors declare there are no conflicts of interest related to the article.

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