Editorial

Statin Therapy for Stroke Prevention: Current Status and Controversies

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Abstract: Statin therapy has become one of the most widely prescribed medications in the world because of its efficacy in the primary and secondary prevention of cardiovascular mortality and stroke. Current cardiovascular guidelines recommend statin use in all patients with stroke due to atherosclerosis (non-cardioembolic stroke). Statin therapy at stroke onset is associated with good functional outcome and reduced risk of cardiovascular events after stroke via different mechanisms. These include lipid-lowering effects, platelet aggregation, improved endothelial function, anti-inflammation activity, neuroprotective action, and stabilization of atherosclerotic plaques. Nevertheless, the effects of statin therapy following major stroke are uncertain and data on the optimal dose and intensity are limited. Statins may potentially increase the incidence of overall stroke and fatal stroke in patients with a history of renal transplantation, or regular hemodialysis. There is a need for additional studies since statins benefits do not extend across all etiologic subtypes of ischemic stroke: they are indicated for thrombotic strokes and some, but not all, lacunar, cardioembolic or essential strokes, and they are not suitable for ischemic strokes of unusual etiology.

Keywords: Statin, Treatment, Stroke, Cerebral infarction, Outcome.

INTRODUCTION

In the last decade, statin therapy has revolutionized the management of vascular diseases since becoming one of the most commonly prescribed medications in the world, because of its potent cardio-protective effects on both primary and secondary stroke prevention [1]. Statin therapy reduces the risk of cardiovascular events after stroke via different mechanisms. These include lipid-lowering effects, platelet aggregation, improved endothelial function, anti-inflammation activity, neuroprotective action, and stabilization of atherosclerotic plaques [2-6].

Stroke is a heterogeneous syndrome with multiple underlying pathologies such as atherosclerotic large vessel disease, small vessel disease, cardioembolic stroke, stroke of unusual etiologies and cerebral ischemia of undetermined etiology [7]. Large vessel disease due to atherosclerosis is more likely to have an association with raised LDL and total cholesterol. Consequently, statin therapy is expected to be more beneficial in those with atherosclerosis [1-8].

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial evaluated the effect of statins in secondary prevention of stroke and reported 16% lower risk of recurrent stroke (11.2% versus 13.1%) with 80 mg of atorvastatin daily, compared with placebo in noncardioembolic stroke or TIA (patients with large and small vessel disease). It was the first trial to evaluate the effect of statin in secondary prevention of stroke. The risk of hemorrhagic stroke was significantly higher in the statin group (HR: 2.4), in men (HR: 1.79) and increased by age (HR: 1.42 per 10-year increment) but not significantly in fatal hemorrhagic stroke [9].

Myotoxicity or hepatic toxicity is a cause of potential adverse effects of statin therapy that may limit daily activities. Caution in patients with a history of liver disease or high alcohol intake, a past or family history of muscular disorders, previous muscular toxicity, renal impairment, and hypothyroidism is mandatory. Routine monitoring of liver profile and CK levels at 3 and 12 months is recommended [1].

META-ANALYSIS

Early clinical studies suggested potential effectiveness of statins in ischemic stroke patients with better early outcome (reduced mortality during hospitalization and neurological disability at hospital discharge) [10, 11]. This reinforced the promising results reported in pioneer studies in experimental animal models [1]. Later, favorable outcomes of statins therapy in cerebral ischemia were definitively confirmed by the results of two meta-analyses performed in

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experimental stroke animal models. Both the study of García-Bonilla *et al*. [12] and Baryan *et al*. [13] clearly demonstrated the effectiveness of statins and their neuroprotective role in experimental ischemia (Table **1**).

The impact of statins therapy in cerebral ischemia in humans (Table **1**) was consolidated by the results of different meta-analysis that showed the beneficial aspects although some negative or neutral effects were presented concurrently. The meta-analysis conducted by Cordenier *et al*. [14] indicated that prestroke statins use was associated with a decreased in-hospital mortality, but did not influence the 3 month functional outcomes. NiChróinin *et al*. [15] reported that statin therapy at stroke onset was associated with good functional outcome although warned that caution should be taken in patients receiving thrombolytic therapy. Naci *et al*. [16] found that statins were effective in reducing the incidence of non-fatal strokes but not of fatal ones. Wang et Zhang [17] reported a decline in the incidence of fatal and hemorrhagic strokes but an increased risk in renal transplant patients and those undergoing regular hemodialysis.

GUIDELINES

Current international guidelines for management of acute ischemic stroke recommend statin use in all patients with stroke due to atherosclerosis (non-

Table 1: Meta-Analysis of the Efficacy of Statins in Acute Stroke

Author, year	Title (number of studies)	Results
Cordenier *et al*. [7], (2011)*	"Pre-stroke use of statins on stroke outcomes: a meta-analysis of observational studies" (11 studies)	Pre-treatment with statins decreases in-hospital mortality Increases the risk of developing a symptomatic hemorrhagic transformation in patients treated with thrombolysis. Statins do not influence the 3 month functional outcomes as measured with the mRS.
García-Bonilla L *et al*. [11], (2012)**	"Evidence for the efficacy in animal stroke models: a meta-analysis" (41 publications)	Reinforces the value of statin treatment in cerebral ischemia By type of statin, simvastatin presents greater infarct size reduction. The estimated effect is higher when statins are given as pre-treatment rather than post-treatment Effectiveness is greater when drug is given orally. Higher doses better than lower doses
Baryan HK *et al*. [14], (2012)**	"Systematic review and meta-analysis of the efficacy of statins in experimental stroke" Effect of statins in animal models of focal cerebral ischemia (18 published studies)	Statins administered after middle cerebral artery occlusion have modest efficacy. Statins administered after the onset of experimental ischemia are neuroprotective
NíChróinín DN *et al*. [15], (2013)*	"Statin therapy and outcome after ischemic stroke" (27 studies)	Statin treatment at stroke onset is associated with good functional outcome at 90 days but not at 1 year and with reduced fatality at 90 days and 1 year. In the studies restricted to thrombolysis-treated patients, an association between statins and increased fatality at 90 days is observed. However this association was no longer present after adjusting for age and stroke severity.
Naci H *et al*. [16], (2013)*	"Comparative effects of statins on major cerebrovascular events: a multiple-treatments meta-analysis of placebo-controlled and active comparator trials" (61 trials)	Statins are significantly more effective than control in reducing major cerebrovascular events. Considering individual statins, significant reduction is achieved by atorvastatin, pravastatin and simvastatin as compared with control on major cerebrovascular events. Statins lead to significant reductions in the risk of non-fatal strokes but not of fatal ones.
Wang W and Zhang B. [19], (2014)*	"Statins for the prevention of stroke: a meta-analysis of randomized controlled trials" (18 randomized controlled trials)	Statins reduce the overall incidence of stroke more than placebo. In particular statins show efficacy in reducing the incidence of fatal and hemorrhagic stroke. Statins increase the overall incidence of stroke and fatal stroke in renal transplant recipients and patients undergoing regular hemodialysis

*Clinical studies; ** Experimental studies.

cardioembolic stroke). For instance, the recommendations of the Catalan Neurology Society [18] agree with the 2013 American College of Cardiology and American Heart Association treatment guideline [19], that recommends intensive statin therapy for all patients <75 years old with atherosclerotic cardiovascular disease including ischemic stroke patients.

The European Guidelines on cardiovascular disease prevention in clinical practice [20] recommend the use of statin therapy in patients with non-cardioembolic ischemic stroke or TIA, but statins should be avoided after a hemorrhagic stroke except in the event of concurrent high vascular risk.

MORE EVIDENCES AND CONTROVERSIES

A benefit of statins given pre as well as after stroke onset was seen with a greater magnitude effect with poststroke statins in the Dublin study [1, 21]. Statin withdrawal in acute stroke has been associated with worse outcomes in terms of dependency and neurological impairment and hence, treatment should be continued, except in the event of hemorrhagic stroke.

However, the effects of statin therapy following major stroke remain uncertain and there are conflicting data on outcomes of patients receiving combination therapy with statins and tPA. Statin use at stroke onset may be associated with increased rates of symptomatic intracerebral hemorrhage after intravenous or intra-arterial thrombolysis possibly mediated via antithrombotic effects of statins on endothelium, leucocytes and platelets, and increased levels of endogenous tPA [15].

Furthermore, data on the optimal dose are limited and little is known about comparison of high-intensity versus low/moderate intensity therapy in clinical stroke subgroups. Some authors suggest that cerebrovascular patients should receive intensive therapy (atorvastatin 40-80 mg or rosuvastatin 20-40 mg), but other statins seemed to be not so effective [22, 23].

Some of these questions have been answered by the PROSPER study recently published [24]. This study analyzed a sample of 77,468 ischemic stroke patients statin-naïve at the time of admission, discharged alive from 2007 to 2011. Of them, 54,991 (71%) were prescribed statin therapy at discharge. Statin therapy was associated with a 9% lower hazard of major adverse cardiac events, 28 more days of home time, a 16% lower hazard of mortality and a 7% lower hazard of all-cause readmission in the 2-year post-discharge period; 30.9% were prescribed high-intensity statin therapy at discharge (atorvastatin >40mg, rosuvastatin >20mg, simvastatin 80mg or simvastatin/ezetimibe 10/80mg). Compared with patients who were prescribed low/moderate intensity statins (all other statin agents/doses) there were no statistically significant differences in clinical outcomes in the 2 years following discharge. No evidence of increased risk of hemorrhagic stroke among statin users was found [24].

Little is known about the role of ezetimibe in stroke prevention. A clinical trial reported that reduction of LDL cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily, safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease [25]. In PROSPER study, the simvastatin/ezetimibe (10/80mg) subgroup was included in the high-intensity statin therapy group and no evidence in clinical outcomes was observed when compared to the non-high intensity group [24].

STATIN THERAPY IN THE DIFFERENT ISCHEMIC STROKE SUBTYPES

Some authors consider that benefits of statins extend across all stroke types including cardioembolic stroke [4]. Because most patients survive stroke and die later from myocardial infarction rather than from another stroke or non-vascular disease, stroke patients contribute highly to cardiac deaths. For this reason, it is considered very important to use statin therapy for all stroke patients [1]. However, this statement is inaccurate by the fact that not all stroke subtypes are related to an atherosclerotic mechanism. Thus, most of cerebral infarcts of unusual etiology are due to hematologic diseases (like polycythemia vera, essential thrombocytemia, protein C deficiency, etc.), to inflammatory arteritis (for example, Horton arteritis), to migraine stroke or to arterial dissection [26] and, in these cases, statin therapy is not suitable. Likewise, in cerebral embolisms due to patent foramen ovale, in rheumatic valvular diseases or mitral valve prolapse, to cite just a few, the statins benefit does not appear to be convincing. Strokes of undetermined cause are an etiological subtype wherein statin therapy is controversial. Nonetheless, within that subtype, complex aortic atheroma is an emerging cause of cerebral ischemia which requires a high clinical suspicion [27-29], and once diagnosed, statin therapy

would then be indicated. Finally, it would be interesting to perform a study in the subgroup of patients with lacunar cerebral infarctions: possibly, in patients suffering from microatheromatosis statin therapy might be useful but in those suffering from lipohyalinosis, statins prescription would not be therapeutically justified [30, 31]. Therefore, the statement that irrespective of the etiology of ischemic stroke, use of statins has been associated with favourable outcomes is not accurate, being vague and generic. Statins should be avoided in strokes of unusual case.

CONCLUSIONS

Statin therapy at stroke onset is associated with good functional outcomes. Effects of statins in secondary prevention of ischemic stroke are beneficial, but there were not statistically significant in the prevention of fatal stroke. Moreover, statins may potentially increase the incidence of overall stroke and fatal stroke in patients with a history of renal transplantation, or regular hemodialysis. The benefits of statin therapy differ depending on the stroke subtype: provide maximum effectiveness in atherothrombotic stroke and may play a useful role in patients with lacunar, cardioembolic or essential strokes, but should be avoided in strokes of unusual cause. Furthermore, no real advantages are noted with the use of high-intensity statin doses compared to low/moderate intensity statin use for ischemic stroke prevention. Randomized trials and individual-patient data from large registries will be required to resolve these issues.

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CONFLICTS OF INTEREST

None to be declared

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