Statins, Stroke Outcome, and Stroke Prevention: When Should We Start Treatment?

Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are a group of potent hypocholesterolemic agents that are widely used throughout the world. Many long-term clinical studies have demonstrated that statin therapy is associated with a reduced risk of vascular events—mainly coronary—even in so-called normocholesterolemic patients. Accordingly, guidelines for cholesterol treatment have been and are being modified, particularly for patients with ischemic heart disease (IHD). The magnitude of the effects is large. A recent meta-analysis has demonstrated that a decrease in low-density lipoprotein cholesterol levels by 1.8 mmol/L reduces the risk of IHD by 61% and the risk of stroke by 17%, preventing thromboembolic but not hemorrhagic strokes. The benefit of statins treatment has also been shown for patients with hypertension, diabetes mellitus, severe aortic arch plaques, and for high-risk patients in general. For secondary stroke prevention, however, the data are still somewhat circumstantial and a specific study is underway. In many of the studies, the beneficial effects of the statins were not directly related to their lipid-lowering properties, and data on many other effects of statins is accumulating. On the vascular wall, statins exert vasodilatation and plaque-stabilizing effects by many ways, such as upregulation of endothelial nitric oxide synthase (eNOS), suppression of heightened macrophage activity with subsequent reduced production of several matrix metalloproteins and proinflammatory cytokines TNFα, IL-6, CRP, and reduction of vascular expression of adhesion molecules. Because all these factors enhance the thrombogenic potential of the atherosclerotic plaque, statins have a role in ameliorating this risk. Antiatherogenic properties of statins were demonstrated in retarding intimal medial thickening of the carotid wall, coronary plaque volume, and aortic atherosclerosis. A more rapid clinical effect was recently reported in patients with acute coronary syndrome: early statin administration was associated with reduced ischemic events within the first month of treatment. This effect was explained, at least in part, by a reduction in local inflammation.

For stroke, statin therapy is believed to be effective even earlier, leading to a better functional recovery; animal studies have recently shown the effects of statins on enhanced functional outcome and induction of brain plasticity when administered after stroke, probably by induction of angiogenesis, neurogenesis, and synaptogenesis. Lesion volumes have decreased regardless of cholesterol blood levels. Stroke protection is lost, however, within 2 to 4 days after withdrawal of statins treatment. These acute pleiotropic effects induce neuroprotection throughout several mechanisms including eNOS modulation (by augmenting regional cerebral blood flow), by inhibition of platelet aggregation, and by antiinflammatory effects.

Are these effects also applicable to human beings? A pilot case-referent study has shown a trend for a favorable outcome (earlier discharge to home) in patients pretreated with statins, and a pilot randomized study on the acute effects of simvastatin in ischemic stroke (MISTICS trial) has demonstrated beneficial effects.

In this issue, Martí-Fabregas et al present their experience with statin treatment and stroke outcome in 167 acute stroke patients, of which 18% were pretreated with statins. This was an open study in which patients were included prospectively and followed-up for 3 months. Median National Institutes of Health Stroke Scale (NIHSS) scores at admission were lower in the statin group (5 versus 6) and neurological deterioration was less frequent in this group (3.3% versus 8.1% in the nonstatin group); yet, maybe because of the small sample size, these differences were not significant. At 3 months, statin treatment was found to be independently associated with a favorable outcome. The authors conclude that statins may provide long-term beneficial effects when given before the onset of acute stroke. They state that for maximum benefit, therapy should start within the first few hours of an acute stroke and declare that a randomized controlled study is needed to clarify the importance of statins on stroke outcome.

This article is important in strengthening previous observations; however, because of its nature (observational, unmatched), it still leaves some uncertainties. Apart from the limitations acknowledged by the authors in their discussion, there is also another concern, ie, the lack of information on concomitant treatment. It is possible that other medications confer neuroprotective properties, as has just recently been presented for angiotensin-converting enzyme (ACE) inhibitors. Also, the possibility that patients using statins are those that get, or can afford, better medical care was not ruled out.

Why were only 18% of the patients using statins? Given our current knowledge and the list of risk factors in the “control” group, this percent should have been higher. Alternatively, the fact that only 18% of the whole group were using statins suggests that a priori such patients are
somewhat protected from stroke. Additionally, the higher rate of lacunar stroke in the treated group may imply that patients with large artery atherothrombosis are more protected because of the pleiotropic and plaque-stabilizing effects of statins.

This study provides information relating to the long-term beneficial effects of statins on stroke outcome, including, perhaps, an additional benefit at the subacute stage; however, this does not clarify the acute effects of statins and the importance of its administration in the hyperacute stage. Thus, the exact timing of statin administration in acute stroke remains open.

In the near future, however, with the completion of the SPARCL study, it may be possible to answer 2 major questions: (1) are statins beneficial in the secondary prevention of stroke in all patients regardless of their premorbid conditions; and (2) are stroke outcomes in the statin-treated group milder and/or associated with a better outcome once they have occurred? We will also be able to learn which subtypes of strokes are mostly influenced by statins.

Within a few years, it seems that most high-risk patients will be treated with statins (the introduction of a “polypill” including a statin has been recently suggested for those patients), and thus only for a minority of the stroke patients will we be facing the dilemma of when to start treatment.

Nonetheless, the importance of the pleiotropic effects of statins in acute stroke should be investigated in a prospective randomized study.

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References
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