Statins and Cerebral Vasomotor Reactivity  
Implications for a New Therapy?

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A
nimal models have shown that cholesterol-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (commonly called statins) may augment absolute cerebral blood flow (CBF) by enhancing nitric oxide synthase (eNOS).1 Statins upregulate type III endothelial eNOS in thrombocytes, decrease platelet activation, and protect from cerebral ischemia in normocholesterolemic mice.2 Statins may also provide additional beneficial effects by upregulating endogenous tissue plasminogen activator and enhancing clot lysis in a mouse model of embolic focal ischemia.3 Statins given 24 hours after experimental ischemia can enhance CBF, angiogenesis, neurogenesis and sinaptogenesis.4 How can these findings be applied in the clinical setting? A meta-analysis of published clinical trials showed that low-density lipoprotein–lowering with statins may decrease the risk of stroke in diabetic or hypertensive patients with normal low-density lipoprotein cholesterol at baseline, and in patients with coronary artery disease, with respectively 48%, 27% and 25% reduction in stroke incidence.5

Does any relationship exist among statins and cerebral vasomotor reactivity? Functional transcranial Doppler (TCD) ultrasonography permits the assessment of cognitively induced CBF velocity changes6 and the evaluation of cerebral vasomotor reactivity.7 TCD can be used to reliably evaluate age-related changes in the physiological response of the human cerebral circulation. A diminished nitric oxide–mediated cerebral vasomotor response may exist in aging subjects and in patients with vascular risk factors.8 Because there are no reliable markers for the functional status of the cerebral small vessels in elderly patients at risk of stroke, TCD studies may be useful. Although some parameters like von Willebrand factor, factor VIII, fibrinogen, and C-reactive protein may be associated with an increased vascular risk, the predictive value is low.9

Cerebral vasomotor reactivity to L-arginine, measured by TCD, is thought to reflect cerebral endothelial function. Observational studies have shown that intravenous infusion of L-arginine induces vasodilatation and significantly increases CBF velocity in the middle cerebral artery in healthy volunteers.10 This physiological effect may be caused by an increased production of nitric oxide because L-arginine is a substrate of eNOS, which produces nitric oxide. L-arginine may improve impaired CO₂ reactivity of the cerebral vessels,11 and endothelial dysfunction in hypercholesterolemic patients.12 An impairment of L-arginine–mediated vasoreactivity has been described in patients with recent stroke.13 Vasomotor response to CO₂ and L-arginine in patients with severe internal carotid artery stenosis is significantly lower on the stenotic side, and improves after endarterectomy.14 Cerebral vasomotor reactivity to L-arginine has been reported to be impaired in patients with lacunar infarctions and in high blood pressure subjects, too.15

Sander et al reported an improvement of cerebral vasoreactivity in healthy adults after short-term statin administration.16 They measured the mean CBF velocity of both middle cerebral arteries by simultaneous bilateral TCD sonography in 25 healthy adults before, during and after administration of pravastatin 40 mg as compared with healthy control persons. The cerebral vasomotor reactivity significantly increased after statin administration on day 7 as compared with the initial value. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)17 trial examined the effect of pravastatin 40 mg on the decline in CBF in elderly subjects at risk for cerebral vascular disease. PROSPER trial showed no effects of daily pravastatin treatment on total CBF or parenchymal volume loss in elderly.

However, statins may beneficially act on cerebral vasomotor function. Results from 2 phase-II randomized placebo-controlled clinical trials using pravastatin 40 mg18 and simvastatin 80 mg19 indicate that the use of statins after aneurysmal subarachnoid hemorrhage may be safe and ameliorate cerebral vasospasm, improve cerebral autoregulation and protect against delayed cerebral ischemia. However, the question of whether the decreased incidence of vasospasm will translate into improved functional outcome needs a better definition.

Can the results of clinical and observational studies be extrapolated to ischemic stroke patients? This question remains to be determined. Wardlaw et al20 suggested that cerebral small-vessel endothelial dysfunction may contribute to the development of lacunar stroke and leukoaraiosis. The leakage of plasma components into the vessel wall and surrounding brain tissue could lead to neuronal damage. Acquired and/or genetic abnormalities in the eNOS might also increase susceptibility to vascular endothelial damage. According to Warlaw's hypothesis, the initial step for most lacunar ischemic strokes might be the failure of the arteriolar endothelium. Patients with isolated lacunar infarction and lacunar infarction plus white matter
lesions may have elevated systemic plasma markers of endothelial activation.21

If we accept that altered vasoregulation may be an important pathogenic mechanism in patients with cerebral small-vessel disease leading to white matter hyperperfusion, recurrent lacunar infarction and vascular dementia, the following question that arises is: may statins help to restore blood-brain barrier and improve endothelial dysfunction? A previous observational study by Sterzer et al22 provided the first evidence for a significant improvement of cerebral vasomotor reactivity by using statins in patients with cerebral small-vessel disease. In this study, CBF velocity increase after bolus injection of 1 g acetazolamide was determined before and after 2-month treatment with pravastatin 20 mg. Although no control group was included, a significant CBF velocity increase was observed after pravastatin therapy.

The study by Pretnar-Oblak et al23 in this issue of Stroke provides some insights into the pathophysiology of cerebral small-vessel disease and the mechanism of action of statins on cerebral vasomotor reactivity. The effect of atorvastatin treatment on cerebral endothelial function, as measured by the response to L-arginine reactivity on TCD, in 18 multiple lacunar stroke patients, 20 age- and gender-matched long-standing hypertension and hypercholesterolemia patients, and 19 gender-matched healthy control subjects was studied. As expected, baseline L-arginine reactivity was decreased in patients with lacunar stroke and vascular risk factors compared with healthy controls. After 3-month atorvastatin treatment, decreased L-arginine reactivity and flow-mediated dilatation significantly improved in both type of patients.

Should the nitric oxide–mediated statin effects be interpreted as a potential mechanism for the prevention of ischemic stroke? Caution and new studies urge, as it cannot be concluded that statins should be used for the prevention of small vessel disease. The results of this interesting article22 add more questions that should be resolved in double-blind, placebo-controlled, randomized clinical trials. Might the effect of statins differ according to stroke subtypes? Can the response to L-arginine reactivity differ among first single and multiple lacunar infarction patients? Should magnetic resonance studies be performed to assess lacunar infarction location and the presence of white matter disease abnormalities in statin-treated patients? Other questions have yet to be defined, such as the optimal dosage of statins in the clinical setting as in observational and experimental studies, too. Dose escalation and efficacy/safety studies are needed.

Finally, there are some common flaps to many cerebral vasomotor reactivity observational studies: (1) small sample size; (2) neither randomization nor blinded outcome assessment were used in case selection; (3) existence of selection bias in control group; (4) absence of estimation of statistical power (1-β); (5) other potential bias including anxiety disorders and comorbid conditions were not controlled. These methodological issues should be taken into account in the future, as they could partially invalidate the findings of many functional TCD studies.

The results of observational studies about the pathophysiological effects of statins on cerebral vasomotor reserve should be considered with caution. The expanding indications for statins in cerebral ischemia24 should be supported by evidence-based medicine analysis. Further studies are required to determine whether chronic treatment with statins can improve white matter lesions, cerebral vasomotor reactivity and prevent the risk of recurrence of lacunar infarctions.

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