Statin discontinuation: counterbalancing the benefits with the potential risks

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Besides cholesterol lowering, statins exert several non-lipid (so-called "pleiotropic") actions [1-4]; statins improve vascular endothelial function and exert antithrombotic and anti-inflammatory effects [1, 2]. Statins are also associated with a reduced incidence of coronary risk and cardiovascular events [5-7].

A recent study demonstrated that statin withdrawal increased the risk of subarachnoid haemorrhage by > 60% compared with non-use (odds ratio (OR) 1.62; 95% confidence interval (CI) 0.96-2.73) and by > 2-fold compared with current use (OR 2.34; 95% CI 1.35-4.05) [8]. An earlier study showed that, compared with continuous statin use, statin withdrawal is associated with an almost 3-fold increase in first-year mortality rates after an ischaemic stroke episode (hazard ratio (HR) 2.78; 95% CI 1.96-3.72; $p = 0.003$) [9]. Finally, a controlled randomized study showed that statin withdrawal at the time of admission for a hemispheric ischaemic stroke was associated with a 19-fold increase in the risk of early neurological deterioration compared with previous statin non-use (HR 19.01; 95% CI 1.96-184.09; $p < 0.001$) [10]. It was proposed that, once initiated, statin treatment should not be interrupted except for a very good reason [11].

The inferior outcomes associated with statin withdrawal may be attributed to a "rebound" phenomenon [11]. Statins inhibit NAD(P)H oxidase and superoxide production and upregulate the expression and activity of endothelial nitric oxide synthase (eNOS) via inhibition of geranylgeranylation of RhoA and Rac1 GTPases [12]. RhoA negatively regulates eNOS and Rac1 contributes to NAD(P)H-oxidase activation and superoxide production [12]. Withdrawal of statin treatment leads to an overshoot activation of RhoA and Rac1 with considerable effects on nitric oxide bioavailability, NAD(P)H-oxidase activity, and superoxide production [12]. The net result is overt endothelial dysfunction and vasoregulatory dysfunction [11, 12].

Besides the studies showing an association between statin withdrawal with subarachnoid haemorrhage [8], mortality rates after an ischaemic stroke episode [9] and neurological deterioration after an ischaemic stroke episode [10], a contradictory report should also be mentioned [13]. This report underlines the increased incidence of intracranial haemorrhage associated with high statin dosage use in patients with a prior history of stroke [13]. A more recent study, however, failed to verify the association

between statin use in patients with a history of ischaemic stroke with an increased risk of intracranial haemorrhage [14]. Current evidence also indicates that statins should be discontinued in patients after a haemorrhagic stroke episode [15]. The 2011 Updated Society for Vascular Surgery guidelines for the management of carotid artery stenosis patients recommended statin use in all patients scheduled for carotid revascularization aiming at reducing low-density lipoprotein cholesterol (LDL-C) levels < 100 mg/dl [16]. Due to these controversial reports, in patients suffering an ischaemic stroke, the possibly increased risk of future intracranial haemorrhage should be counterbalanced with the expected cardiovascular benefits associated with statin use.

Ideally, the exact effects of statin withdrawal should be investigated in a prospective randomized trial. Given the uniform results from the reports performed so far, however [8-10], such a trial may never be carried out due to considerable ethical limitations. Physicians should ensure that patients not on statins initiate a statin immediately after a vascular event [11] or prior to vascular surgery [17]. More importantly, however, they should make sure that patients on routine statin use do not discontinue their treatment in order to avoid the occurrence of a first [8] (or recurrent) [9, 10] vascular event.

Unfortunately, there is evidence that many cardiovascular patients do not receive any lipid-lowering treatment [18]. Some physicians may be reluctant to prescribe lipid-lowering drugs in all patients, independent of their lipid levels. They should bear in mind that serum LDL-C levels < 70 mg/dl do not seem to affect the adrenal axis function in terms of cortisol production, which is mainly synthesized from cholesterol [19]. Thus, physicians may administer statins independently of the patient's lipid levels.

These data suggest an increased physician alertness for statin discontinuation in vascular patients.

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