Editorial

Statins and Tissue Plasminogen Activator for Stroke: A Beneficial Combination?

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Interruption of the blood supply in the brain leads to irreversible tissue damage in the ischaemic core, whereas the regions with less severe blood perfusion deficit include potentially salvageable tissue which gradually evolves into infarction in the absence of reperfusion [1]. Thus, the ischaemic penumbra is a clinically relevant therapeutic target.

The evolution of ischaemic brain damage is a heterogeneous and dynamic process involving several cell types and molecular events [2-4]. Statins, commonly used for the treatment of hypercholesterolaemia and atherosclerotic disease, exert several pleiotropic actions such as: anti-inflammatory, anti-proliferative, antioxidant, anticoagulant, antiplatelet and immunomodulatory effects [2, 5-9]. They are used for both primary and secondary prevention of coronary heart disease and stroke [10-16]. Several studies documented that statins administered acutely after stroke, can improve clinical neurological outcomes and prognosis [14, 16]. Moreover, statin discontinuation is associated with worse post-stroke survival [17, 18]. Clinical studies reported that tissue Plasminogen Activator (tPA) increases oxidative stress and inflammatory responses which mediate reperfusion injury and damage after stroke [18]. tPA crosses the blood-brain barrier (BBB) and may induce neurovascular disruption and parenchymal damage, reducing the beneficial effects of thrombolytic therapy [19]. In this context, the co-administration of statin and tPA is controversial. Zhang *et al*. [2], reported that atorvastatin abolishes tPA-induced aggravation of BBB disruption downregulating the expression of endothelial matrix metalloprotease (MMP)-2 and MMP-9. A prospective multicentre study (2, 072 patients) documented that the administration of a statin in the acute phase of stroke after thrombolysis may positively influence short- and long-term outcome without any increase in haemorrhagic transformation [14]. In agreement, Campos *et al*. [20], reported that statin use in stroke patients treated with tPA is associated with favourable clinical outcome, without the development of brain haemorrhage. In a pooled observational study of 11 thrombolysis databases, Engelter *et al*. [21], evaluating 4, 012 stroke patients receiving thrombolysis, documented that the use of statins does not increase the frequency of parenchymal haemorrhage. In contrast, Meier *et al*. [22], evaluating 311 patients on intra-arterial urokinase, documented a higher frequency of haemorrhagic transformation in 55 patients treated with statins. Capellari *et al*. [23], showed that in 178 patients, treatment with statins started until 24h after intravenous (i. v.) thrombolysis improves stroke outcome, whereas the prophylactic treatment with statins is associated with an increased risk of haemorrhagic transformation. Meseguer *et al*. [24], in 11 clinical studies (6, 438 acute stroke patients) evaluating the effect of statin use on outcomes after thrombolysis, did not find a beneficial or detrimental effect of prior statin use. Recently, Scheitz *et al*. [25], evaluated 1, 446 acute stroke patients in 2 European *i.v.* thrombolysis registries and documented an association between increasing dose of statin use and risk of haemorrhagic transformation in 317 (22%) patients treated with statins before i. v. thrombolysis. However, statin users more often achieved favourable outcome compared with non-statin users. The effects of statins on blood coagulation have been reported by Undas *et al*. [26]; they documented that statins reduce thrombin generation and modify fibrinolytic balance by up-regulating endogenous tPA production and reducing plasminogen activator-inhibitor-1 expression. This might lead not only to enhanced efficacy of tPA, but also to an increased risk of brain haemorrhage. However, the effect of statins on coagulation is controversial [27] and could be related to the type of statin used. Recently, a meta-analysis reported a decrease in plasma D-dimer levels after 3 months of statin therapy, especially after using lipophilic compared with hydrophilic statins [28].

It is not possible to exclude that any increased risk of brain haemorrhage during the co-administration of statin and thrombolysis may be related to patient characteristics. Statin users are more likely to be older, men, on polytherapy and have a history of stroke, diabetes mellitus and hypertension compared with non-statin users [21].

Tsivgoulis and *et al*. [29], evaluating 1, 660 acute ischaemic stroke patients treated with i. v. thrombolysis documented that patients with statin pre-treatment had higher baseline stroke severity compared with patients who had not received a statin. After adjusting for potential confounders, statin pre-treatment was not associated with a higher likelihood of symptomatic intracranial haemorrhage or to 3-month all-cause mortality. However, higher odds of early clinical recovery were independently associated with statin pre-treatment. In agreement, Geng *et al*. [30] assessed the effect of statins after i. v. alteplase, within 24 h of

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acute ischaemic stroke (71 of 119 patients given a statin). Treatment with statins in the early stage of ischaemic stroke was safe and did not increase the risk of intracerebral haemorrhage.

To date, even if the co-administration of statin with tPA might increase the risk of brain haemorrhagic transformation, the magnitude of this adverse event appears to be low, while the discontinuation of statins after acute stroke may be associated with a worse clinical outcome. Research on the effects of co-administration of statins and tPA (e. g. time of treatment, dosage and type of statin) could confirm the efficacy and safety of this treatment option.

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