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INVITED COMMENTARY

Statins in Subarachnoid Hemorrhage to Prevent Delayed Cerebral Ischemia: Old Drugs for New Strategies?

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Subarachnoid hemorrhage (SAH) caused by a ruptured cerebral aneurysm is probably the most devastating event that can affect the brain. It is a predominantly medical condition, which, after the initial intervention that stops the bleeding (clipping or coiling), can go on to an important sequela of complications. The tools available to the intensivist physician are relatively few. Undoubtedly, the most fearsome complication is delayed cerebral ischemia (DCI), defined as the occurrence of focal neurological deficits or loss of at least 2 points on the Glasgow Coma Scale not attributable to other causes. DCI manifests neuroradiological as an area of ischemic distress that evolves into an infarct and is often the consequence of vasospasm of large vessels. Few drugs and treatments are available to reduce the risk of DCI (e.g., nimodipine, blood pressure manipulation). Among the many tested drugs, much has been written about the function of statins, most notably, an antispastic effect on affected vessels through activation of endothelial nitric oxide expression. The most up-to-date guidelines on SAH (2023 American Heart Association/American Stroke Association and Neurocritical Care Society) do not recommend statins in these patients because of the lack of studies and literature reviews strong enough to demonstrate efficacy on DCI and mortality.

In 2014, a large randomized trial conducted by Kirkpatrick et al. [1], the Simvastatin in Aneurysmal Subarachnoid Hemorrhage trial, enrolled 803 patients with SAH, assigning them to the "simvastatin" group and the "placebo" group. The follow-up lasted 6 months, and the authors established that taking a statin did not improve short-term or long-term outcomes. In the study results, even more patients in the intervention group died than in the control group, and favorable outcomes did not differ in the two groups [1].

Wang et al. [2] performed a network meta-analysis on the effects of different statin agents in patients with SAH, concluding that 40 mg of pravastatin and 80 mg of simvastatin significantly reduced the risk of DCI. Unfortunately, the certainty of evidence ranged from low to moderate. The analysis includes 13 randomized trials, identified on databases PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. Different doses of atorvastatin, pravastatin, and simvastatin versus a placebo treatment administered to a total of 1,885 patients for different durations of administration (2 or 3 weeks) were analyzed. The follow-up period present in these analyzed studies was different (1–6 months), and some studies lacked specifics about it. The outcomes considered were mortality, functional outcome, and DCI. Among these, only DCI was shown to correlate with statin administration. From the results of the analysis, it appears that in the patient treatment with statins (40 mg of pravastatin and 80 mg of simvastatin), 2 weeks were sufficient. Because of insufficient data, the authors could not perform subgroup analysis or meta-regression. For this reason, the findings need to be accepted cautiously before translating them into everyday clinical practice [2]. There is one specific element that is not transferable to clinical practice worldwide from the study by Xing Wang et al. [2]: the administration of 80 mg of

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simvastatin is off-label to European and North American drug agencies; in contrast, 40 mg of pravastatin turns out to be the standard dose normally prescribed. Moreover, these drugs are only available as an oral preparation, and this might need to be addressed before their use could become widespread in critical patients.

The REMAP-CAP Investigators compared simvastatin (80 mg daily) with no statin in critically ill patients with coronavirus disease 2019 who were naive to the drug [3]. Simvastatin therapy has anti-inflammatory and immunomodulatory effects, but the previously mentioned trial failed to demonstrate superiority to standard care with respect to organ support–free days and death. Nevertheless, the incidence of adverse events correlated to simvastatin therapy, for example, elevated levels of creatine kinase and liver aminotransferases were higher in the simvastatin group (3%) than in the control group (2%).

Is the use of statin safe in critical patients? The main contraindications to the use of statins are muscle symptoms, which are undoubtedly the most recurrent side effects of chronic statin administration, but very often they are the result of patient and physician misinterpretation of the manifest symptom, causing their overestimation. Instead, through a more comprehensive analysis of the side effects of statins, obviously measured against a chronic administration for patients with dyslipidemia, it is possible to state that there is a modest increase in new-onset diabetes mellitus, whereas there is no association between statin therapy and cognitive dysfunction or clinically deterioration of renal function or development of cataract. Transient increases in liver enzymes occur in 0.5–2% of patients taking statins but are not clinically relevant. However, the common side effects of statin, liver dysfunction and myositis, are particularly relevant in sepsis because deterioration in liver function occurs during the early course of sepsis. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network investigators demonstrated that rosuvastatin did not improve survival or ventilator-free days in patients with sepsis-associated acute respiratory distress syndrome and may have contributed to hepatic and renal organ dysfunction. Finally, there is no evidence of an increased risk of hemorrhagic stroke in individuals without cerebrovascular disease [4]. On the contrary, preinjury statin use may contribute to mortality reduction in patients with traumatic brain injury, whereas statin withdrawal might increase mortality [5].

The importance of the Simvastatin in Aneurysmal Subarachnoid Hemorrhage trial results has probably limited enthusiasm for statins in these patients. However, focusing on mortality and final outcome, very often influenced by quite other factors, seems a very lofty goal. If efficacy will be demonstrated on the incidence of DCI with any degree of evidence, which affects a fraction of these patients, the statin could be a new/old arrow in our quiver. It could be very important measuring the incidence of DCI in patients with SAH who were already chronically assuming statin for other indications.

Finally, to update the international guidelines on SAH management, a new randomized trial comparing 40 mg of pravastatin, 80 mg of simvastatin, and a placebo treatment for 2 weeks and that also considers DCI among the outcomes is undoubtedly needed.

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References

1. Kirkpatrick PJ, Turner CL, Smith C, Hutchinson PJ, Murray GD; STASH Collaborators. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. Lancet Neurol. 2014;13(7):666–75.
2. Wang X, Gan Q, You C, Ma L. Effect of statin treatment in patients with aneurysmal subarachnoid hemorrhage: a network meta-analysis. Neurocrit Care. 2024. https://doi.org/10.1007/s12028-024-01957-9.
3. Hills TE, Lorenzi E, Berry LR, Shyamsundar M, Al-Beidh F, Annane D, et al; REMAP-CAP Investigators. Simvastatin in critically ill patients with covid-19. N Engl J Med. 2023;389(25):2341–54.
4. Mach F, Ray KK, Wiklund O, Corsini A, Catapano AL, Bruckert E, et al; European Atherosclerosis Society Consensus Panel. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. Eur Heart J. 2018;39(27):2526–39.
5. Susanto M, Siahaan AMP, Wirjomartani BA, Setiawan H, Aryanti C, Michael. The neuroprotective effect of statin in traumatic brain injury: a systematic review. World Neurosurg X. 2023;19:100211.