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Letter to Editor

On antithrombotic mechanisms of statins: Are they relevant in intracerebral or subarachnoid bleedings?

I have read with interest a review by Kotlęga and colleagues [1]. The authors summarized the current clinical and experimental data on the links between the use of statins and intracranial bleeds, precisely intracerebral and subarachnoid hemorrhages. They drew a firm conclusion that there is no compelling evidence that indeed statins may increase bleeding risk in neurological patients at risk of cardiovascular disease receiving this highly effective class of drugs to reduce blood cholesterol levels. Evidence on the link between the statin use and bleeding is inconsistent and a very recent meta-analysis of randomized controlled studies showed that higher daily doses of statins are associated with an increased risk of intracerebral hemorrhages [2]. However, these findings did not affect the current recommendations in patients with acute ischemic stroke or transient ischemic attack. It is widely accepted that stroke prevention involves lifestyle modification and specific treatment, including among others the use of statins and other lipid-lowering drugs [3]. High-dose statins are of key importance in stroke prevention among patients with asymptomatic carotid stenosis [4].

The review did not pay attention to potential mechanisms through which statins may increase bleeding risk of various locations, including intracerebral bleeds. It is worth mentioning that based on various experimental studies, statin therapy may favorably alter several steps of the blood coagulation cascade [4]. Through down-regulation of tissue factor expression on monocytes and vascular cells as well as enhanced thrombomodulin expression on endothelial cells, statins reduce thrombin generation and increase the activity of the protein C anticoagulant pathway leading to lower amounts of activated factor V generated following injury, which contributes to reduced FXa-mediated prothrombin activation [5]. Consequently the final result of statin use is decreased fibrinogen cleavage and thrombin-mediated platelet activation [5] and there is no rationale to rule out these systemic anticoagulant effects in all vascular beds. Importantly, anticoagulant effects of statins can be observed as early as after 1–3 days of their administration [6]. Moreover, statins have profibrinolytic effects including decreased plasminogen activator inhibitor type 1 (PAI-1) expression and formation of less compact fibrin clots that are more susceptible to lysis [5]. Favorable modulation of a fibrin structure and function, including loose fiber network, in subjects receiving statins is a novel antithrombotic effect of these drugs, which are to some extent related to their thrombin lowering actions. Of note, despite the fact that statins were reported to have anticoagulant properties, we found that bleeding rates were not significantly different in statin-users versus non-users. On the other hand, Schmidt et al. reported that statin use, along with oral or parenteral anticoagulation, was associated with approximately 25% reduction in the risk of recurrent venous thromboembolism at 3-year follow-up, without increasing the risk of bleeding [7]. Taken together, anticoagulant and profibrinolytic effects of statins are subtle and detectable locally mostly in response to vascular injury; they do not significantly increase bleeding risk in everyday practice. As suggested in the review [1], the overall effect of statins on hemostasis, regardless of their dosage, supported by interrelated anti-inflammatory, antioxidative and immunomodulatory actions, appears beneficial in terms of thromboembolic events [5]. Given however growing experimental data and ongoing clinical large trials on the use of statins in subarachnoid hemorrhage, a delicate hemostatic balance nicely modulated by statins should be carefully observed and especially the administration of these agents at a moderate-to-high doses in the early phase of such hemorrhages might lead to clinically evident prohemorrhagic effects. This effect is likely to limit the everyday use of statins in patients hospitalized for intracerebral and subarachnoid hemorrhages.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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