Title: **Statins after intracranial haemorrhage: seizing a new opportunity?**

Article Type: Commentary

Related Article: Lin HW, Ho YF, Lin FJ. Statin Use Associated with Lower Risk of Epilepsy after Intracranial Hemorrhage: A Population-Based Cohort Study.

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Word count total (main text): 1120

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bcp.13754

References: 7

Key Words: Statin; intracerebral hemorrhage; hemorrhagic stroke; epilepsy

The use of statins in patients following ICH remains controversial; despite the demonstrated beneficial effects of statins in preventing first-ever and recurrent ischaemic stroke, the rate of prescription is variable,[1] which could in part be because of concerns about a potentially increased risk of intracerebral hemorrhage (ICH). Whether any increased ICH risk might outweigh the benefit of statins is particularly controversial in patients with a previous ICH; as well as lipid-lowering, statins have other (pleiotropic) actions, including antiplatelet and anticoagulant effects. Furthermore, in both the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) and Heart Protection Study (HPS), the benefit in reducing recurrent ischemic stroke was offset in part by an increased risk of ICH.[2-4] Another potentially interesting effect of statins in ICH survivors (who are at substantial risk of post-stroke seizures)[5] is their potential to reduce epileptogenesis by several mechanisms: (i) attenuating the link between the NMDA receptor subunit-1 and lipid rafts, which may protect against NMDA mediated excitotocitity; (ii) restoring the balance of pro-inflammatory cytokines (IL-1β, TNFα and IL-6) in favour of anti-inflammatory cytokines (IL-10); and (iii) exerting beneficial effects on endothelial dysfunction through normalising vasomotion. Indeed, some observational studies reported a lower risk of epilepsy in older people or those with ischemic stroke, which could relate to statin exposure.

In the British Journal of Clinical Pharmacology, Hung-Wei Lin and colleagues performed a cohort study of the impact of statins in patients with ICH on the risk of post-stroke epilepsy in a Taiwanese prospective population-based inception cohort study of adults with first-ever ICH.[6] Of the 7,435 participants included with ICH, 597 (8%) were using statins prior to the event, while 868 (11.6%) started statins during follow-up. In keeping with previous study

post-ICH epilepsy rates, 709/7,435 (9.5%) developed epilepsy over a median follow-up of 17.6 months, in the majority (57.2%) within 6 months post-ICH. Amongst pre-ICH statin non-users, of those who developed post-ICH epilepsy 5.5% (36/659) initiated statins during follow-up compared with 13.4% (832/5,347) who did not develop post-ICH epilepsy. After statistical adjustment, post-ICH, but not pre-ICH, statin use was associated with a reduced risk of epilepsy (HR 0.62, 95% CI 0.42-0.90). A dose-response relationship was identified, where both a higher statin dose and higher intensity statin were associated with greater reductions in post-ICH epilepsy (HR 0.37, 95% CI 0.18-0.75). Although lipophilic statins were statistically associated with reduced post-ICH epilepsy (HR 0.63, 95% CI 0.40-0.98), hydrophilic statins were not statistically associated (HR 0.59, 95% CI 0.30-1.16) although the similar hazard ratio point estimate suggests that this difference might be explained by the limited sample size.

The study was of good methodological quality, including population-based recruitment with clear presentation of the event incidence with minimal attrition. A reasonable selection of covariates was included in the multivariate regression model and the use of several sensitivity analyses helped confirm that the current results are likely to be specific to statins and post-ICH epilepsy.

However, there are some study limitations that could affect the conclusion that statins reduce post-ICH epilepsy. First is the mixture of intracranial haemorrhage types included because the authors defined of ICH was based on the ICD-9 codes 430, 431 and 432, which includes subarachnoid, intracerebral, and "other and unspecified intracranial hemorrhage", all of which have different causes and might have different seizure risks. However, some reassurance is provided by their sensitivity analysis including patients diagnosed with intracerebral

hemorrhage only (ICD-9 code 431, which accounted for about 74% of patients with intracranial bleeding). The relatively crude ICD-9 classification system also limits investigation of the impact of statins on the underlying causes of intracerebral hemorrhages. Most ICH is due to two broad types of disease affecting cerebral small vessels: hypertensive arteriopathy, which affects deep perforating vessels; and cerebral amyloid angiopathy (CAA), which affects superficial cortical and leptomeningeal vessels. While hypertension is the strongest risk factor for deep ICH (mostly mediated through hypertensive arteriopathy), a substantial proportion of lobar ICH are due to CAA, with a high recurrence risk (7·4% per year [7]) and late seizure risk due to cortical involvement[5]. Interestingly hypertension, a known major risk factor for ICH, was linked to a lower risk of post-ICH epilepsy, even after adjustment for severity and antihypertensive medication. Although this may be explained by ICH related to hypertension (and hypertensive arteriopathy) being frequently located in the deep brain structures (which might be less likely to cause seizures than lobar ICH), it could also relate to methodological aspects including the way different comorbidities and therapies were coded.

Second, the study was unable to clarify the temporal sequence of events of patients with ICH who were started on statins and newly diagnosed with epilepsy within the same hospital admission. Although the authors did sensitivity analyses excluding patients with early seizures (within 14 days) post-ICH, it is still possible that some patients receiving statins after the observed seizures could have been miscoded. Furthermore the authors do not report recurrent ICH or death rates, raising the possibility that the reduced epilepsy rate amongst statin users was in part due to competing risks of recurrent ICH and death in the statin exposed patients.

Most importantly, despite the attempts to adjust for relevant covariates, the study could still be subject to important sources of bias, including residual confounding by important factors that influence seizure risk, for example cortical involvement or ICH volume, because these were not available in the claims database used for the analyses. Statins might be less likely to be recommended by physicians after severe large-volume ICH with high seizure risk (due to the poor prognosis), which could contribute to an apparently protective effect of statin use. Moreover, as statins are prescribed when clinicians detect presence of cardiovascular disease risk factors, treatment with statins in this observational study is likely to be related to the probability of vascular events including ICH, creating confounding by indication. Indeed Table 1 highlights the significant differences in baseline characteristics between statin users and nonusers. Finally, healthy user bias could mean that patients receiving statins have other healthy behaviors, e.g. exercise, diet, alcohol, etc. which could bias the apparent protective effect for statins on seizures.

Nevertheless, this paper is important in suggesting that statins might have unexpected and beneficial effects on seizure risk (and thus potentially function and quality of life) in ICH survivors. An important next step is thus to perform future randomised trials of statins in ICH survivors to clarify their overall safety and efficacy. These trials should assess a wide range of clinical endpoints, including all-cause mortality and functional measures but also further clarify the impact on future ICH risk and post-ICH epilepsy. Further contentious questions should also be addressed including: (i) which statin; (ii) what dose; (iii) when to initiate; (iv) and when to withdraw.

Competing interests: **OJZ** has no relevant conflicts. **DJW** was UK chief investigator for A9951024 (Pfizer), and has received consultancy fees from Amgen and lecture fees from Bayer.

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