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Stroke: do statins improve outcomes after acute ischemic stroke?

Joshua Z Willey[1] and **Mitchell S V Elkind**[1,2]

[1]Department of Neurology, Columbia University, New York, NY

[2]Department of Epidemiology, Columbia University, New York, NY

Stroke remains the leading cause of serious disability among adults in the United States[1]. There is only one treatment that is approved by the United States Food and Drug Administration for AIS for improving functional outcomes, recombinant tissue plasminogen activator, but few receive it or have access to it due to strict exclusion criteria[2]. Thus, there is considerable interest in finding other agents that may improve functional status after AIS. Pre-clinical data provide multiple possible mechanisms of action for statins that could lead to improved functional outcomes after ischemic stroke, including promotion of angiogenesis, preventing neuronal cell death, or modifying inflammatory and coagulation pathways[3]. Statins are readily available and are well tolerated by most patients with a benign side effect profile, further making these agents an attractive target for treatment after acute ischemic stroke. Biffi, et al, attempt to answer the interesting question of whether treatment with statins is associated with improved functional outcomes after acute ischemic stroke (AIS). Previously published reports have usually been limited to small sample sizes, heterogeneous choices for the definition of a good functional outcome after AIS, and potential publication bias in favor of only positive studies. The authors used their experience at the Massachusetts General Hospital and then performed a meta-analysis of previously published results to further explore whether statins improve functional outcome after AIS.

In the first part of this study the authors investigated the effect of statins on functional outcome in patients who arrived with AIS to their institution within 24 hours of onset. A good functional outcome was defined by a modified Rankin scale of 0-2. Among a total of 893 patients, 126 were taking statins at the time of their AIS; these patients were more likely to have hyperlipidemia, as well as a history of anti-hypertensive medication use, tobacco use, and to drink alcohol. Treatment with statins before AIS onset was not associated with 90-day favorable outcome or mortality. In pre-specified analyses they found that statins were associated with improved outcomes among the 102 patients with small vessel disease (odds ratio 1.97, 95% confidence intervals 1.02-3.79), though only 10 of those were taking statins.

In the meta-analysis the authors combined 11 previous publications ranging from single-center experiences, to population based studies, to one clinical trial. The inclusion of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) was problematic however since it was not an AIS trial[4]. In SPARCL participants were not eligible until 30 days after their initial event. The total number of patients in the meta-analysis was 2013 statin users and 9682 non-statin users, and again the authors found that antecedent treatment was associated with improved functional outcomes for all strokes (odds

Standfirst: Using data from their site, and a meta-analysis of prior studies, the authors found that being on statins before ischemic stroke was associated with an improved functional outcome. In the meta-analysis however they found possible evidence of publication bias in favor of small studies with positive results.

ration 1.62, 95% confidence interval 1.39-1.88), as well as in only large artery and small vessel etiologies. The authors however cautioned against drawing significant conclusions from their meta-analysis, and their subsequent bias analysis was particularly informative. A "small study effect" was suspected and proven such that studies with largest effect size were also the ones with the smallest sample sizes. Publication bias was hypothesized to be one possible explanation such that studies with negative results would not be published, and demonstrated their hypothesis through accepted statistical techniques. In conclusion the authors concluded that their results suggested a possible association between statin use before AIS and functional outcome.

The study had particular strengths, including focusing on ischemic stroke, and in particular on stroke subtypes, rather than lumping all strokes (including hemorrhagic together). The possible protective effect of treatment on functional recovery after stroke may be different depending on the cause of stroke. The investigators had a large sample size, and were appropriately cautious in the interpretation of their results given their exploration of selective publication bias. Several unanswered questions remain with this analysis, the most important of which is whether patients would be helped by administration of statins in the acute stroke setting. Unfortunately this study, or the others that were included in the meta-analysis, do not allow us to answer that question. In the studies included in the meta-analysis the outcomes and inclusion criteria were heterogeneous, making comparability of the studies difficult to interpret. For example some studies defined a good outcome as a modified Rankin scale 0-2, while others used 0-4 or another functional outcome scale. The choice of the outcome could have significant implications on whether a treatment is found to be helpful or not. Furthermore each study also includes a different time frame for the outcome, from 7 days after AIS to 90 days after AIS. The analysis was limited to efficacy, but did not comment on safety outcomes, or whether or not patients who receive intravenous tissue plasminogen activator can also be given statins; this may not be a trivial point if statins are associated with risk of hemorrhage[5]. In this meta-analysis we also cannot answer the question of how statins may improve functional outcomes after AIS. The authors hypothesized that the pleiotropic effects of statins may be why these agents are helpful, but they also are clearly protective against recurrent stroke and myocardial infarction which could also explain the improved functional outcomes. Lastly whether the patient was taking a statin before their stroke is not a random occurrence, and factors that were not captured in the referenced studies could be associated with both treatment with statins and functional outcomes leading to an erroneous conclusion of an association. The analysis by Biffi et al does add to the evidence that statins may benefit AIS patients, but the limitations of their study and the presence of possible publication bias, limits to what degree we can apply it to our patients. Whether AIS patients should receive statins within 24 hours can only be answered with a randomized clinical trial.

Author biographies

Joshua Z. Willey, Assistant Professor of Neurology, Columbia University. Dr. Willey has a clinical practice in neurology with a focus on cerebrovascular diseases and stroke. His research has focused on risk factors for clinical and subclinical cerebrovascular disease in the Northern Manhattan Study under the mentorship of Dr. Elkind. He is a member of the American Academy of Neurology, and the American Heart Association.

Mitchell S. V. Elkind

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Boxes

-There is only one approved medication to reduce disability after acute ischemic stroke, recombinant tissue plasminogen activator, but few are eligible to receive it.

-Statins have several plausible mechanisms of action for how they could improve functional outcomes in patients with acute ischemic stroke, and are readily available

-In this meta-analysis investigators demonstrated that an antecedent statin was associated with a good functional outcome after acute ischemic stroke.

-The results however should be interpreted with caution and clinical trials are required to establish whether treatment with statins in the acute setting improves outcomes in patients with acute ischemic stroke.