Editorial

Statins and aneurysms

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As a class of agents originally developed to lower serum cholesterol as a treatment for cardiac atherosclerotic disease, statins have since been studied extensively in a variety of neurological syndromes. They have shown promise in reducing the morbidity of intracerebral hemorrhage and perihematomal edema and have been postulated to possess a neuroprotective effect in the setting of ischemic stroke and neurotrauma.\(^1\) With respect to subarachnoid hemorrhage (SAH), statins seem to reduce the risk of vasospasm and delayed ischemic deficits while decreasing overall mortality.\(^2,3\) The mechanism of action of this class of medications is quite extensive and involves antioxidant, anticoagulant, antiinflammatory, and profibrinolytic effects.\(^1\) Findings in animal models have indicated that statin treatment may reduce the incidence of aneurysm formation through several mechanisms, including inhibition of macrophage migration, a vascular protective “pleotropic” effect through attenuation of intravascular inflammation, and improved endothelial function through upregulation of nitric oxide synthase.\(^4\)

In the current study, Marbacher and colleagues\(^4\) perform a single-center case-control study to investigate whether the use of statins can inhibit intracranial aneurysm formation. The study design is unique in that patients admitted to the authors’ institution with the diagnosis of an intracranial aneurysm (IA) are compared with randomly selected patients without IAs who were matched for the usual characteristics. The authors’ primary interest is exposure to statins prior to hospital admission. The vast majority of the patients with IAs presented with SAH (265 ruptured and 35 unruptured cases). The authors include more than 1200 patients in this study and, in performing a careful statistical analysis, conclude that there is no overall association between statin use and intracranial aneurysm incidence. Interestingly, the authors confirm that hypertension and cigarette smoking are independent risk factors for aneurysm formation. These have been identified as independent risk factors in other studies as well and add to the validity of the authors’ primary conclusion that statin use has no effect on IA formation. The authors also report an inverse relationship between diabetes mellitus and SAH, a finding that has been confirmed in other studies.\(^2,3\)

Much of the excitement regarding potential beneficial effects of statins in preventing aneurysm formation is derived from studies involving the development of abdominal aortic aneurysms.\(^9,10\) As the authors note, clinical studies attempting to demonstrate a reduction of aneurysm growth in patients receiving statins have not shown significant benefit. The therapeutic effect of statin use in preventing cardiovascular events may be related to the dose of the drug and the duration of use. It is quite possible that the present study is not sufficiently powered to detect a difference between such heterogeneous study groups, given that the study population was divided rather simplistically between patients with a short (<12-month) or long (>36-month) duration of pretreatment with statins. The inclusion of both ruptured and unruptured aneurysms in the same study is also somewhat problematic. The factors that contribute to the development, growth, and rupture of IAs have yet to be clearly defined, and such heterogeneity in a retrospective study (with all of its other potential inherent sources of bias) adds to the difficulty of teasing out a positive result regarding statin exposure. Nevertheless, the study is an important addition to the literature and may temper enthusiasm for statin use as a cure-all for all manner of neurological disorders. Large multicenter trials with varying doses and lengths of administration to identify what is likely to be a modest beneficial effect may be needed.

Disclosure

The authors report no conflict of interest.

References

Editorial


Response

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We appreciate the comments made by Drs. Bambakidis and Selman on our article. We agree that the inclusion of both ruptured and unruptured intracranial aneurysms is somewhat problematic. Our hypothesis was that statins might have an effect on both aneurysm formation and the risk of rupture. The initial pathophysiological changes leading to the formation of an aneurysm are still not fully understood. Ruptured and unruptured aneurysms may share a common pathophysiology, at least in the very early stages of formation. Thereafter, however, it is likely that the biology of ruptured and unruptured aneurysms is different. After the initial event of formation, the aneurysm may be highly unstable and prone to rupture, but it stabilizes over a short period of time. Alternatively, aneurysms may primarily develop into two different entities, one prone to rupture and the other much more stable as shown by the International Study of Unruptured Intracranial Aneurysms (ISUIA).1 We agree that the potential effects of statins may vary between these two entities. In our study, we included more ruptured aneurysms than unruptured aneurysms (8:1), and we believe that a statin effect on ruptured intracranial aneurysms is more relevant.

We also agree that our study was not sufficiently powered to detect differences between subgroups in this heterogeneous study population. However, concerning the overall effect of cumulative statin exposure on aneurysm formation, we think that these data are rather robust and the likelihood of detecting an association, even by doubling the study population, remains low. Our rationale is further supported by an odds ratio of 1.08 (CI 0.69–1.69) for the effect of statin use on aneurysm formation; this was far from a borderline statistical value. Admittedly, we must assume an estimated 2% (12 patients) of undiagnosed incidental intracranial aneurysms in the control group. However, to remove them from the control group, we would have had to perform imaging for the diagnosis of IAs in all control individuals, which was not possible given the retrospective nature of the study. To address this issue, we tested the influence of this variable on the overall findings, and assigned these 12 patients as either a 100% statin user or nonuser. Ultimately, the robust odds ratio changed only marginally. As pointed out by Drs. Bambakidis and Selman, the “cure-all” statins might not be the miracle drug for IAs.

Reference


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