Commentary

Reduced Risk of Intracerebral Haemorrhage from Statins: Added-Value of Large Healthcare Data

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Rigorously designed randomised controlled trials can provide reliable estimates of the effects of treatments, but they generally involve carefully defined and selected patients, in which a limited range of demographic, clinical and disease variables are measured over a relatively short period of follow-up. Conversely, large population databases can complement the evidence generated from clinical trials by allowing associations to be made between treatments and a broad range of sociodemographic, clinical and management variables over long periods of exposure in a variety of health conditions. A good example of the latter is outlined in the article of this issue of EClinicalMedicine, where Ribe and co-authors [1] report results of a retrospective, Danish population registry-based study, undertaken to address the longstanding controversial clinical issue of whether statins increase the risk of intracerebral haemorrhage.

The results of the international Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial published in 2006 [2] had a major influence on guidelines and clinical practice for secondary stroke prevention across the globe. Although substantial benefits of high dose of atorvastatin were shown to reduce the risk of future serious ischaemic vascular events in patients with cerebrovascular disease, post-hoc analyses further indicated that the treatment was associated with an increased risk of intracerebral haemorrhage (hazard ratio [HR] 1.66, 95% confidence interval [CI] 1.08–2.55). Despite subsequent systematic reviews of the accumulated evidence [3–5], the mixed results of SPARCL cast a lingering doubt over the net benefit of statin treatment, particularly in certain clinical (e.g. those with prior intracerebral haemorrhage) and population (e.g. Asians) groups considered at high risk of intracerebral haemorrhage.

Ribe and colleagues [1] sought to determine the risks of intracerebral haemorrhage and ischaemic stroke following the initiation of statin treatment in 519,894 individuals without a history of stroke, who were propensity-matched by age, sex and calendar year, to five control non-statin users over a 10-year period from 2004. After controlling for a wide range of sociodemographic and medical covariates, including the use of antithrombotic and antihypertensive agents, the primary findings were of reduced risks of both intracerebral haemorrhage (adjusted HR 0.85, 95% CI 0.8–0.9) and ischaemic stroke (HR 0.96, 0.94–0.99) after six months of treatment, and for the risk reductions to increase with a longer duration of statin use.

Key strengths of this study include the minimum influence of selection bias by the inclusion of a whole population, the completeness of follow-up and reliability of endpoint diagnoses against standard medical coded definitions and the large sample size that allowed various multivariable analyses in which there was consistency of the results in various sensitivity analyses according to different outcome definitions, follow-up period, and varying lengths of carryover and grace periods from the time of prescription.

A key limitation of such observational studies, however, is just that of the ‘association of factors’, where incomplete adjustment for known and unknown covariates restricts the inferences that can be made about treatment effects. Other issues relate to ‘healthy initiator’ (statins are more likely to be initiated in robust individuals), ‘indication’ (statins are more likely to be initiated in those considered at high risk of ischaemic vascular events), and ‘participant’ (healthier patients are more likely to continue taking statins) biases; which Ribe and colleagues argue were not clearly apparent in their analyses.

Finally, all research studies face the challenge of accounting for the influence of potential interactions between different medicines and the motivation of participants to take them as well as adhere to healthy lifestyle behaviours. What is absolutely clear, though, is the benefits derived from good adherence to the recommended triple strategy – blood pressure lowering, statins, and an antithrombotic agent – in high risk people will clearly offset the associated potential tiny risk of intracerebral haemorrhage [6]. In the absence of direct randomised evidence specifically in patients considered at high risk of intracerebral haemorrhage, the work of Ribe and colleagues should help to provide further reassurance over the safety and benefits of statin treatment.

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Authors Contribution

CA wrote this article.

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