Reviewer's report

Title: Comparison of statins for secondary prevention in patients with ischemic stroke or transient ischemic attack: a systematic review and network meta-analysis

Version: 0 Date: 27 Oct 2018

Reviewer: David Spence

Reviewer's report:

You must not say that statins cause intracerebral hemorrhage; this is a myth that has been perpetuated for too long.

Statins do not cause intracerebral hemorrhage; this is confirmed in two previous meta-analyses.[1, 2] The whole controversy is an artefact resulting from the ITT analysis of SPARCL,[3] in which 25% of patients randomized to placebo crossed over to statin, and many patients discontinued statin. They should have provided an on-treatment analysis. Low levels of LDL-C do not cause ICH; this is now clear from the studies of PCSK9 antibodies, with LDL-C down to 0.2 mmol/L (~ 7.6 mg/dL).[4]

The increase in ICH in patients randomized to statin in SPARCL could not have been due to statin, because the patients who had ICH did not have lower LDL-C.[5] It is not possible to not have a lower LDL-C when taking atorvastatin 80mg. The participants who had ICH had higher blood pressures, and were significantly more likely to have Stage 2 hypertension.[5] The reason they had ICH was probably because when they had an adverse effect of statin on the study, they went off all their medication (as patients so often do), including their blood pressure medication. When this reviewer called Michael Welch, the PI of SPARCL, about this at the time SPARCL was published, his response was "You are a very astute clinician."

In patients with very low levels of LDL-C in statin trials, neither a prespecified safety analysis of the Improve-it trial[6] nor the large meta-analysis (n = 170,000) of intensive lipid-lowering with statins[7] found no increase in intracerebral hemorrhage with statins. When the authors of the latter paper added the SPARCL trial and two other trials to a meta-analysis shown in the supplement, they found a small though statistically significant increase in ICH. However, they estimated that the risk of ICH from statins is ~ 50 times lower than the benefit than the benefit from taking statins. That estimate was predicated on a mistaken conclusion that statins slightly increase the risk of ICH: they don't. This means that it is probably much more than 50 times higher risk to stop statins than continue them in stroke patients, who are at high risk of vascular events.

You found more hemorrhagic strokes because you studied statins in secondary prevention in patients with stroke or TIA, who are more likely to have ICH. However, ICH is due to hypertension, and can be eliminated in secondary stroke prevention by good blood pressure control. In the NASCET trial, local site PIs received a stiff letter whenever blood pressure medication was not increased in a patient whose blood pressure was above the protocol target
blood pressure at a followup visit. Intracranial hemorrhages, including subarachnoid hemorrhage and lobar hemorrhage, were only 0.5% of strokes in the medical arm of the study, at a time when ~ 20% of strokes were due to ICH in most populations. You must control for blood pressure in assessing ICH in your study; you should also repeat your meta-analysis without the SPARCL trial, and since you are focusing on differences between statins, make it clear that it was only because of the ITT analysis of SPARCL that it seemed that statins cause ICH.

If possible, you should analyse prevention ischemic stroke by stroke subtypes; statins reduce stroke by more in large artery disease.[8]

As you have shown, effects of statins are class effects; for the most part there are no differences among statins. However, one issue should be mentioned: lovastatin and simvastatin, because they are only 5% bioavailable, have a huge potential for drug interactions with grapefruit or with many drugs that inhibit intestinal CYP3A4. Plasma levels (the AUC) of simvastatin increase 15-fold with potent inhibitors of CYP3A4; plasma levels of atorvastatin (bioavailability 50%) only double with inhibitors, and pravastatin and rosuvastatin are not affected. [9] A case of rhabdomyolysis was reported in a woman on simvastatin 80 mg daily, 4 days after she began eating one grapefruit a day.[10] Simvastatin and lovastatin are unsafe drugs, because grocers seldom take a drug history when dispensing grapefruit.

Throughout the manuscript, "gender" should be changed to "sex":


"Sex" refers to the biological and physiological characteristics that define men and women.

"Gender" refers to the socially constructed roles, behaviours, activities, and attributes that a given society considers appropriate for men and women.


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