Lipid lowering and recurrent stroke: another stroke paradox?

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This editorial refers to 'Plasma lipids predict myocardial infarction, but not stroke, in patients with established cerebrovascular disease' by A. Patel et al., on page 1910

The meta-analysis of over 90,000 patients included in statin trials shows a significant 21% reduction of stroke with no heterogeneity between trials and no increase in haemorrhagic stroke. Because the link between total cholesterol and incident stroke has never been clearly established in epidemiological studies, it is surprising to see, in the meta-analysis, that the larger the between-group LDL level difference the greater the stroke risk reduction. Indeed, we calculated that LDL reduction could explain 35–80% of the benefit of statins on stroke risk reduction, leaving room for other non-lipid lowering effects of statins, the so-called pleiotropic effects, but the main effect is through LDL reduction.

New results from randomized trials since this meta-analysis, have confirmed that LDL lowering decreased the risk of stroke in diabetics with 'normal' LDL cholesterol at baseline and in patients with coronary artery disease (CAD), with 48 and 25% reduction in stroke incidence, respectively. In the Treat to New Target trial, the benefit was observed in the group of patients with a mean LDL cholesterol of 70 mg/dL when compared with the group of patients with a mean LDL level of 1.02 mg/dL. Hence, the lack of a relationship between cholesterol and stroke in epidemiologic studies is paradoxical because the association between carotid atherosclerosis and blood cholesterol has been well established in other epidemiologic studies, and carotid atherosclerosis is a true cause of stroke. This paradox is explained in part by the design of epidemiologic studies which did not take into account the aetiologic heterogeneity of stroke. Combining ischaemic and haemorrhagic strokes may mask a true relation between ischaemic stroke and high blood cholesterol, because haemorrhagic strokes seem to have an inverse relationship with blood cholesterol.

Blood cholesterol and recurrent stroke, another paradox?

Patel et al. performed a nested case-control study. Cases were 895 patients with incident ischaemic and haemorrhagic strokes or myocardial infarctions (MIs) occurring throughout the follow-up of the PROGRESS trial and controls were matched in the remaining patients without recurrent event among the 6105 patients included. Cases and controls were compared for baseline total cholesterol. After adjustment association between total cholesterol and ischaemic stroke, haemorrhagic stroke, and MI was, respectively, 1.06 (0.92–1.24), 0.72 (0.47–1.12), and 1.44 (1.15–1.81), and after adjustment association with the third tertile was, respectively, 1.00 (0.76–1.33), 0.66 (0.31–1.40), and 2.00 (1.30–3.09). In this analysis, the authors did not find an inverse relationship of ischaemic stroke with HDL cholesterol either.

Blood cholesterol lowering and recurrent stroke, is this effective?

These new data from the PROGRESS trial show no evidence that recurrent ischaemic stroke is predicted by baseline total blood cholesterol, although it predicts MI. Indeed, the HPS trial that looked at cholesterol lowering in a subgroup of 3000 patients with stroke prior randomization found no effect in reducing recurrent stroke, with 10.4% stroke in the simvastatin group and 10.5% stroke in the placebo group after 5 years of follow-up. In these patients, however, the HPS trial did find a significant reduction in major coronary events. These results fit perfectly well with the data reported. Even in the PROSPER trial, which looked at LDL cholesterol lowering in 6000 elderly subjects at risk (50% with risk factors and 50% with established vascular disease including 12.5% with stroke prior to randomization), there was no effect on stroke incidence after 3 years of follow-up. However, PROSPER investigators did not have the power they were looking for because they expected a stroke event rate of 8% per year and they observed 4%, and they followed the patients for 3 years, although in all other positive pravastatin trials, the effect on stroke incidence started to appear after the third year and was significant at 5 or 6 years.

However, in the HPS trial, patients with stroke prior randomization were included in the study an average 4.3
years after their stroke event. This is a time when patients have a very low risk of stroke and are at a high risk of MI. It is thus possible that the HPS trial did not have the power to find a true effect of LDL cholesterol lowering in preventing recurrent stroke. Only a dedicated trial, such as the SPARCL trial, may give a definite answer. The SPARCL investigators included 4732 patients with brain infarction or transient ischaemic attacks and no history of MI within 6 months after their stroke event, at a time where the expected stroke rate is very high and the MI rate is very low. In this trial, we will be in a position to capture all early recurrent strokes occurring within the first 4 years after stroke onset, which has not been the case in the HPS trial. The results should be announced by mid-2006.

Is there a true stroke paradox?

When a study is not designed to answer a specific question, we should always take post hoc analyses with caution, even if the analyses are best performed, such as in the present paper. However, looking at the figures in the paper, we see that the relationship between ischaemic stroke and total cholesterol, although not significant, is in the right direction. We can further expect that the relationship with LDL cholesterol (data not shown) is even more in the right direction because the Friedewald formula \( [\text{LDL} = \text{TC} - (\text{HDL} + \text{TG}/5)] \) subtracts one-fifth of triglycerides which are in the opposite direction on the graph. It is, for example, possible that if the authors have taken ischaemic stroke subtypes into account they would have found an association with atherothrombotic strokes (which accounts for only 30% of all strokes). Classifications into aetiological ischaemic stroke subtypes may help identify the most likely underlying pathologic disease, e.g. atherothrombotic disease, or a more heterogeneous group of diseases, e.g. cardioembolic diseases (gathering valvulopathy, CAD, atrial fibrillation) and brain infarction of unknown cause, which is certainly the most heterogeneous group. I believe that this approach is important in studying risk factors, such as hypercholesterolaemia, which could be associated with a single disease (e.g. atherothrombotic brain infarction or lipohyalinosis) and contrasts with other approaches which consist in studying larger but heterogeneous groups of patients (e.g. with 'ischaemic stroke').

PROGRESS lipid analyses cannot be taken as an epidemiological study because recruitment depended on inclusion criteria of a therapeutic trial aimed at blood pressure lowering. It may be that increasing statin prescriptions throughout the trial modified the profile of stroke recurrence, that patients on statins (the ones more likely to have high cholesterol at entry or documented atherosclerotic disease) had less recurrent strokes. It would have been perhaps necessary that the authors adjust on statin prescriptions during the trial (not only prior to the trial, as has been done) and on the presence of carotid stenosis at randomization.

Cholesterol and stroke: the jury is still out

These new data from the HPS and PROGRESS studies as well as pending data from very large epidemiologic cohort and from the SPARCL trial will shed new light on our understanding of the complex causal relation between cholesterol and stroke. Indeed, it is hard to believe that this relationship is not causal, because there is a strong causal association between cholesterol and carotid plaques and because statins significantly reduced carotid atherosclerosis, which is a true cause of stroke. Only specific epidemiologic studies looking at the pathogenesis (e.g. incident atherosclerotic ischaemic strokes) will be able to provide a definite answer.

References