EDITORIAL

The “‘Other Revolution’” in Stroke Prevention

In the past, several well known clinical trials have shown the potential benefits of carotid endarterectomy over best medical treatment, for selected groups of patients with carotid atheroma. The results of these trials are still cited to set the standard of treatment even nowadays after significant modifications in the diagnostic workup, improvements in anaesthesiological and surgical care and after the carotid artery stenting revolution. In recent years however, another revolution has taken place, possibly one of the most important advances in stroke prevention since the introduction of anti-platelet and pressure-control medications.

There are indeed many studies in the literature regarding the contribution of lipids to stroke risk, however conclusive evidence is still lacking. This is due, at least to some extent, to the design of most of these studies that do not consider the heterogeneity of strokes and investigate only total cholesterol. For instance, the PSC observational study that followed 450,000 subjects for 16 years, failed to find an association between cholesterol and stroke risk, yet it should be noted that only total cholesterol and only fatal strokes were evaluated regardless of the aetiology (ischemic/haemorrhagic); actually probably only 20% of strokes are immediately fatal and patients with non-fatal strokes are more likely to die later from myocardial infarction than from another stroke. On the other hand, in the MRFIT study (over 350,000 men studied), that included analysis of stroke subtypes, a clear relationship was found between serum cholesterol and the risk of ischemic stroke. In the Hisayama population based study (2351 subjects followed for 19 years) athero-thrombotic and lacunar strokes were significantly increased with increasing levels of LDL cholesterol. In recent systematic reviews, HDL cholesterol was associated inversely with stroke risk and evidence of a positive association of triglyceride levels and stroke was found.

Amarenco and Labreuche recently published on “Lancet Neurology” an interesting meta-analysis of statins for stroke prevention that included over 165,000 high-risk individuals pooled from 24 randomized trials with at least 1000 patient each. The original trials were published between 1994 and 2009; they included the major statins such as “atorvastatin”, “lovastatin”, “pravastatin”, “rosuvastatin”, and “simvastatin”, in combination with other preventive strategies. The most recent JUPITER and SEARCH trials were included in this study.

The meta-analysis showed a consistent 18% reduction of all strokes in patients randomized to statins. It also showed that each 1 mmol/L (39 mg/dL) decrease in LDL cholesterol equates to a reduction in relative risk for stroke of 21.1% (95% CI 6.3–33.5, p = 0.009). In secondary prevention of non-cardioembolic stroke, intense reduction of LDL cholesterol by statins also significantly reduced the risk of recurrent stroke (relative risk 0.84, 0.71–0.99, p = 0.03) and major cardiovascular events (0.80, 0.69–0.92, p = 0.002). The lower the LDL cholesterol concentration, the greater is the risk reduction for both primary and secondary prevention of stroke.

On the other hand the incidence of fatal stroke was reduced by 13% (−3 to 27, p = 0.10), and this did not reach statistical significance. Statins showed a good overall safety profile: the incidence of haemorrhagic stroke did not increase (RR 1.03, 95% CI 0.75–1.41, p = 0.88); without evidence of heterogeneity across the trials, and only two trials (HPS, SPARCL) of secondary prevention of stroke suggested an increased incidence of hemorrhagic stroke. Due to the results of these two studies however, caution was recommended when considering statin therapy in patients with prior cerebral haemorrhage.

A different population based study was carried out in Japan on 30,802 men and 60,417 women, 40–79 years of age with no history of stroke or coronary heart disease; they completed a baseline risk factor survey in 1993 and mortality surveillance was performed through 2003. Persons with LDL cholesterol ≥140 mg/dL had half the sex- and age-adjusted risk of death due to intra-parenchymal haemorrhage of those with LDL cholesterol <80 mg/dL. LB Goldstein has addressed the complex relationship between cholesterol and brain haemorrhage in an interesting editorial published in the same recent issue of Circulation.

In spite of the fragile evidence regarding the relationship between cholesterol and stroke risk, several previous studies in addition to Amarenco’s recently updated meta-analysis also showed that a reduction of cholesterol with statins is correlated with a decrease in the incidence of stroke in selected groups of patients. Furthermore, statins slow the progression of carotid atherosclerosis reduce inflammation and endothelial dysfunction and decrease the risk of thrombo-embolic brain events by reducing the incidence of myocardial infarction.
"Carotid plaque stabilization" are by no means empty words, a recent study hosted on this Journal\(^1\) showed that intensive lipid-lowering therapy with atorvastatin administered for 6 months in patients with carotid artery stenosis \(>40\%\) but without indication for intervention, ameliorated carotid plaque echogenicity quantified by the Gray-Scale Median (GSM) score which has been previously associated with plaque vulnerability.

In most statins trials, there is much emphasis on the outcome of major coronary events alone; therefore the overall benefits of statin therapy are often underestimated. In particular it has now been shown unequivocally that statins reduce the risk not just of coronary events but also of strokes in a wide range of subjects (including women). Making sure that patients at high risk of any type of occlusive major vascular events achieve, and sustain, a significant reduction in LDL cholesterol would probably produce major clinical and public-health advantages.\(^8,11\) Raising HDL cholesterol concentrations and lowering triglyceride concentrations may also play a role in stroke prevention and are worth further investigation.

We are all aware that guidelines for indication of treatment for patients with carotid atheroma still rely largely on studies performed when 1) ultrasonography was not very reliable and could not offer an accurate analysis of the plaque, 2) surgery was still burdened by mortality and morbidity rates that would nowadays be considered unacceptable at most institutions, 3) carotid stenting did not exist. At the present time however we cannot ignore the "other" revolution in stroke prevention: the key role of statins in lipid management.

References

3 Prospective studies collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. Lancet 1995;346:1647–53.