SERUM CHOLESTEROL LEVELS, HMG-COA REDUCTASE INHIBITORS, AND THE RISK OF INTRACEREBRAL HEMORRHAGE: THE MULTICENTER STUDY ON CEREBRAL HEMORRHAGE IN ITALY (MUCH-ITALY)

Background
Low serum total cholesterol levels have been inconsistently associated with an increased risk of symptomatic intracranial hemorrhage (ICH), and the contribute of HMG-CoA reductase inhibitors (statins) therapy to this relationship is unclear.

Methods and Results: As part of the Multicenter Study on Cerebral Hemorrhage in Italy (MUCH-ITALY) we compared 3,492 consecutive patients with ICH (mean age, 73.0 ± 12.7 years; males, 56.6%; 1,888 deep ICH) with 3,492 stroke-free control subjects frequency-matched with cases for sex and age. Hypercholesterolemia was inversely associated with ICH, independently of potential confounders. Increasing levels of cholesterol were associated with a decreased risk of ICH (average OR, 0.88; 95% CI, 0.86 – 0.89, for every increase of 0.26 mmol/l of total serum cholesterol concentrations). Conversely, statin use was directly associated with ICH risk (OR, 1.51; 95% CI, 1.29 – 1.75, at the average level of total serum cholesterol). There was statistical interaction between total serum cholesterol levels and statin use for the risk of hemorrhage [Interaction odds ratio (IOR), 1.08; 95% CI, 1.05–1.12, for ICH regardless of hematoma location] with no independent effect of statins. Statin therapy turned out to reduce the protective effect of total serum cholesterol against ICH, especially in cortico-subcortical regions.

Discussion
The question of whether serum lipids, including cholesterol, might be linked to ICH, and whether cholesterol-lowering drugs might be involved in this relationship has been matter of long debate, and existing reports conflict with one another. In particular, it is still unclear whether statin use may confer an increased risk of cerebral bleeding. In line with a number of prior reports, we observed that total serum cholesterol concentrations were inversely associated with the risk of ICH. Our findings also suggest that statin use before the index event might be associated with higher odds of intra-cerebral bleeding. Furthermore, we found differential patterns of associations depending on the location of the hematoma, the strongest effect of statins being detected in the subgroup of patients with strictly lobar haemorrhage. We cannot dispute the fact that the potential risk of ICH associated with statin use, if any, is unlikely to overshadow the large benefits conferred by lipid-lowering medications in reducing cardiovascular events, including ischemic stroke. Nevertheless, clinicians should carefully consider bleeding risk when prescribing statin therapy targeting low cholesterol levels.