Statistical plan for: Imaging della Placca Carotidea (IMPLAC) study

The primary outcome of the study will be the presence of white matter hyperintensities (WMH) progression (defined as the appearance of at least 1 new lesion on cerebral magnetic resonance imaging) after 18 months. The secondary endpoint will be the reduction of brain volumes (total volume, grey matter volume and white matter volume) at 18 months. Our primary analysis will be focused at identifying independent predictors of WMH among clinical characteristics of the patients as well as plaque related variables, including volumetric measures of plaque volumes and characteristics of plaque vulnerability, such as presence of ulcer or neovascularization. All continuous variables will be tested for normality using Shapiro-Wilk normality test and are expressed as mean±standard deviation (SD) or median [interquartile range (Q1-Q3)] as appropriate. Categorical variables are summarized as absolute frequency (percentage). Group differences will be tested using unpaired t test, Mann-Whitney U test or Wilcoxon matched pair signed rank test. Spearman's rank correlation coefficient was used to assess statistical dependence. Association between categorical variables was tested using Chi-squared test or Fisher's exact test as appropriate. A $p<0.05$ was considered significant. A multivariate regression analysis was then performed to identify factors that independently influence the burden of WMH in terms of number and volume. All variables associating to WMH burden with a $p<0.10$ will be included in the multivariable model. Our main hypothesis is that subjects with a high plaque burden will experience the highest progression of WMH. We calculated the sample size for multivariate logistic regression analysis with a power of 0.8 and an alpha of 0.05. We will analyze the highest tertile of carotid plaques burden in terms of plaque volume versus others (see Sillesen, 2012). By this definition, the prevalence of high burden atherosclerosis will be 33%. We estimated a clinically relevant probability of progressing in terms of WMH in the high burden group to be 50%, while subjects without high burden plaques are estimated to progress in terms of WMH as the general population with carotid atherosclerosis in a similar time frame. This probability would be estimated to be around 15% (see Dufoil, 2005 and Pico, 2002). The estimated sample size would be 58 individuals. All statistical analyses will be performed using GraphPad Prism 5 (GraphPad Software Inc., La Jolla, USA), IBM SPSS Statistics 20 (IBM, Armonk, USA) or R v3.1.2.