# A MRI study into the effect of pravastatin on cerebrovascular pathologies

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# 1. General Introduction

White matter hyperintensities and cerebral infarcts are commonly observed on magnetic resonance imaging (MRI) of the brain in elderly subjects [1]. Contrary to cortical infarcts, white matter hyperintensities and lacunar cerebral infarcts have been thought for a long time to be benign findings, but nowadays many studies have shown that they predict cognitive decline, dementia, and depression [2, 3].

White matter hyperintensities in the brain are considered to be a manifestation of cerebrovascular disease [4, 5]. These lesions represent pathologic changes in the white matter, and are located in the periventricular and deep white matter structures of the brain. Cerebral infarcts can also be detected using MRI and are either located in the cortical grey matter and/or the cerebral white matter and named subcortical infarcts. In many studies white matter hyperintensities and cerebral infarcts have been associated with various vascular risk factors, except serum cholesterol [6], figure 1.

Clinical stroke before the age of 70 is equally due to cerebral hemorrhages and cerebral infarcts. After the age of 70, the incidence of cerebral infarcts strongly increases, while the incidence of cerebral hemorrhages is unchanged [7]. Although serum cholesterol is not a risk factor of stroke, pooled data on the effect of HMG-CoA reductase inhibitors (statins) show a 30 % risk reduction of strokes in middle-aged patients with ischemic heart disease [8]. Statin treatment has a protective effect on the atherosclerotic process and reduces the risk of coronary heart disease, but the mechanism underlying the favourable effect of pravastatin on stroke risk remains subject to discussion. Considering the heterogeneity of the pathogenesis of stroke, these beneficial results in middle-aged patients can not be extrapolated to the elderly, among whom stroke occurs far more frequently.

In a substudy of the PROspective Study of the Elderly at Risk (PROSPER) we investigated the effect of treatment with pravastatin 40 mg daily on the progression of manifestations of cerebrovascular disease, using magnetic resonance imaging. Recently new magnetic resonance (MR) techniques have become available to investigate the effect of pharmacological interventions on cerebral blood flow and occurrence of cerebral vascular disease. Using these techniques we also

investigated the mechanism underlying the presumed protective effect of pravastatin on stroke risk.

## Aims of the thesis

The more general objective of this thesis was to investigate the etiology of cerebrovascular disease and the role of statin treatment in preventing cerebrovascular disease in non-demented elderly subjects with vascular disease or at increased vascular risk, using magnetic resonance imaging techniques. All subjects that are described in this thesis were participants of the PROSPER MRI substudy. The study design of the PROSPER and MRI study is described in chapter 2.

For the present analyses a new volumetric semi-automated technique for quantification of white matter hyperintensities was developed, as described in chapter 3. A comparison with a commonly used visual rating scale of white matter hyperintensities was performed to assess the reliability of this new method.

In chapter 4, 5, and 6 we report on the possible etiology of white matter hyperintensities and cerebral infarcts. In chapter 4 we describe the association of cardiovascular risk factors with white matter hyperintensities and their impact on the progression of periventricular and deep white matter hyperintensities. In chapter 5 the association between total cerebral blood flow and white matter hyperintensities is reported. In chapter 6 we describe the association of periventricular and deep white matter hyperintensities with the occurrence of new cortical and subcortical cerebral infarcts.

Finally, in chapter 7 and 8 we report on the effect of three years of pravastatin treatment on total cerebral blood flow, white matter hyperintensities and cerebral infarcts. In chapter 7 we describe the effect of statin treatment on cerebral blood flow. In chapter 8 we describe the effect of three years statin treatment on preventing the progression of white matter hyperintensities and occurrence of new cerebral infarcts.

The main conclusions are summarized and discussed in chapter 9.

References


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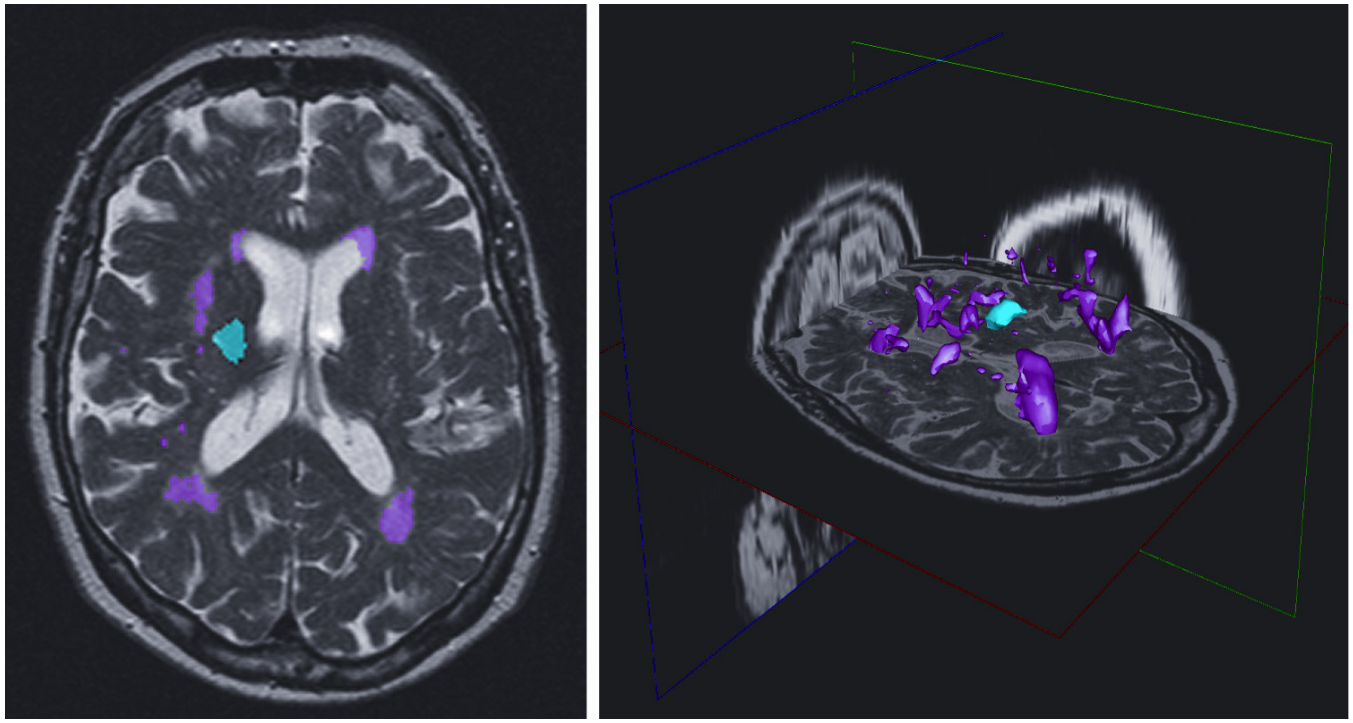

Figure 1: Computerized semiautomated lesion segmentation system for quantifying the volumes (mL) of ischemic brain lesions (Brain-o-Matic). Blue indicates infarction and purple indicates white matter lesions.