A MRI study into the effect of pravastatin on cerebrovascular pathologies

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9. General Discussion

The 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 (MRI) techniques. All subjects were participants of the PROSPER MRI substudy. In the previous chapters the studies were described in detail. In this chapter the results of these studies are summarized and put in a broader perspective. The implications of our findings are discussed and directions for future research are suggested.

Main conclusions

For this study a new volumetric semi-automatic technique to quantify the load of white matter hyperintensities in the brain was developed. A comparison with a commonly used visual rating scale of white matter hyperintensities was performed to show the reliability of this method as described in **chapter 3**. For follow-up studies it is important to use a measurement which is able to detect changes in white matter at repeated measurements with good accuracy. Visual rating scales have ceiling effects and the reliability of these methods is modest. We compared a commonly used visual rating scale (Scheltens' scale) with a new in-house developed volumetric semi-automatic measurement technique. We compared these methods in terms of their reliability and sensitivity to detect changes in volume of white matter hyperintensities with increasing age. Our data suggest that volumetric measurements of white matter hyperintensities offer a more reliable, sensitive, and objective alternative to visual rating scales in studying longitudinal changes of white matter hyperintensities.

Etiology of cerebrovascular disease

Age-related white matter hyperintensities and cerebral infarcts are both presumed to be manifestations of cerebrovascular disease [1-4]. However, the etiology of these two phenomena is not yet completely clear. Neuro-anatomical studies have suggested that periventricular and deep white matter hyperintensities have a different etiology [5-8]. Moreover, several other studies have suggested that cortical and subcortical infarcts have different etiologies [9, 10]. Investigation on the etiology of cerebrovascular disease was the subject of chapter 4, 5, and 6.

In **chapter 4** we described the cross-sectional and follow-up associations between various cardiovascular risk factors and deep and periventricular white matter hyperintensities. In the cross-sectional data a history of hypertension was significantly associated with presence of total and deep white matter hyperintensities. After adjustment for cerebral infarcts, the association between a history of hypertension and total white matter hyperintensities weakened, but the association with deep white matter hyperintensities remained. In the longitudinal analysis, smoking at baseline was significantly associated with progression of total and periventricular white matter hyperintensities during follow-up. Adjustment for presence of cerebral infarcts did not change these results. These results indicate that different pathological processes probably underlie the development of deep and periventricular white matter hyperintensities.

Cerebral blood flow decreases with increasing age, while the incidence of white matter hyperintensities also increases in older age [11, 12, 13]. Total cerebral blood flow is partly determined by brain volume, but atherosclerosis, cerebrovascular disease, and decline of metabolic need of the brain are likely to also play a role in the decline of cerebral blood flow with age. In **chapter 5** we investigated the association between changes in total cerebral blood flow and progression of total, periventricular, and deep white matter hyperintensities over time. We found no association between baseline cerebral blood flow and prevalence of total, periventricular, or deep white matter hyperintensities. A decline of cerebral blood flow was not associated with an increase of total white matter hyperintensities. When we separated total volume of white matter hyperintensities into periventricular and deep, decline of total cerebral blood flow was associated with increase of periventricular but not deep white matter hyperintensities. We therefore concluded that periventricular but not deep white matter hyperintensities may be a manifestation of diffuse cerebrovascular disease in elderly people.

The association between age-related white matter hyperintensities and cerebral infarcts has been reported in several studies [14]. White matter hyperintensities and cerebral infarcts are both manifestations of cerebrovascular disease. However, the etiology of deep and periventricular white matter hyperintensities probably have a

different etiology. Moreover, deep, small cerebral infarcts and cortical infarcts may also have a different etiology. In **chapter 6** we describe the association between periventricular and deep white matter hyperintensities and cortical and subcortical cerebral infarcts. Both periventricular and deep white matter hyperintensities at baseline were strongly associated with subcortical but not cortical cerebral infarcts at baseline. A high volume of baseline periventricular but not deep white matter hyperintensities predicted the incidence of a new subcortical infarct during follow-up. We concluded, based on these data, that periventricular white matter hyperintensities and subcortical infarcts probably have the same etiology, whereas deep white matter hyperintensities and cortical infarcts probably have a different etiology.

Statins and cerebrovascular disease

Ageing is associated with a decline of CBF [11, 12, 13]. The etiology of this age-dependent reduction of cerebral blood flow remains to be elucidated. An increase of 30% of the basal cerebral blood flow induced by statins has been reported in mice [15]. In **chapter 7** we describe the effect of 3 years of treatment with pravastatin 40 mg daily compared to placebo on the decrease of total cerebral blood flow in elderly subjects at risk for vascular disease. We found a significant decrease of cerebral blood flow with increasing age which was explained by a concomitant reduction in brain volume. Both the uncorrected change of cerebral blood flow over time and the change of cerebral blood flow corrected for parenchyma volume were not influenced by pravastatin 40 mg daily. We conclude that treatment with pravastatin during a period of 3 years has no influence on the decrease of total cerebral blood flow and on the progression of cerebral atrophy.

Clinical trials in middle-aged men with coronary heart disease have shown that statins have a beneficial effect on stroke risk [16 17]. It is less clear whether statins decrease the incidence of stroke in elderly subjects. In the very old most infarcts result from cerebrovascular disease, which produces either cerebral arteriolar occlusion or widespread incomplete infarction of white matter. In **chapter 8** we describe the effect of 3 years treatment with pravastatin 40 mg daily on the progression of the volume of white matter lesions and the volume of cerebral

infarcts. Using repeated brain MRI, we found that statins did not prevent cerebrovascular disease, because there were similar progression rates in the total volume of ischemic lesions, white matter hyperintensities, and infarcts in the group treated with pravastatin and the placebo group. We conclude that treatment with pravastatin during three years time does not influence the progression of cerebrovascular disease.

Methodological issues

We performed a longitudinal study with repeated MRI measurements. A longitudinal study design is the appropriate method to assess causality, but several potential distorting issues have to be taken into account. Repeated measurements of volume of white matter hyperintensities should be sensitive and reliable. Until now mainly the visual rating scales have been used for measuring white matter hyperintensities. These methods are hampered by ceiling effects and have modest intra- and interrater reliability. In the present studies, we used a new in-house developed semi-automatic measuring method for measuring the volume of white matter hyperintensities. This method is a more sensitive and reliable alternative to visual rating scales for measuring changes of volume of white matter hyperintensities. We also measured total cerebral blood flow which varies widely between subjects [18]. Hence, a very large number of subjects should be included in order to detect significant associations. However, variation in change of cerebral blood flow within individual subjects is smaller and therefore longitudinal studies are more sensitive to detect small changes.

A difficult problem that occurs in almost all longitudinal studies is the loss of participants during follow-up. In our study 646 participants had a first MRI and 554 participants also had a second MRI. Among the 92 dropouts (14%) causes of attrition were death (n=40), claustrophobia (n=9), a new pacemaker during follow-up (n=3) and withdrawal from the main study (n=7), whereas 34 dropped out because of various illnesses. Compared to the other participants, the 92 participants that were lost during follow-up had higher volumes of white matter hyperintensities at baseline and more often had a history of myocardial infarction. It is therefore likely that we have underestimated the progression of the lesions in

time by missing participants at risk of cerebrovascular disease. The estimate of pravastatin to prevent cardiovascular events is less likely to be affected as pravastatin had no clear effect on all cause mortality.

In this thesis we studied a selected group of older people. All participants were selected on having vascular disease or vascular risk factors. The results of this study may therefore not be easily extrapolated to the general population. Due to our selection on older people with vascular risk factors, the severity of vascular disease in our study is higher than in population-based studies. In our study 39 % of the participants had a brain infarct on MRI at baseline, which is a higher prevalence than in the Rotterdam Scan Study (24%) and the Cardiovascular Health Study (28%) [2, 3]. The selection of our participants at higher risk of vascular disease has provided us with greater statistical power to estimate the efficacy of the pharmacological intervention. However, this selection probably weakened the power for the investigation of the association of cardiovascular risk factors with white matter hyperintensities and total cerebral blood flow. As participants have cardiovascular risk factors, comparison of participants with vascular risk factors and a control group with participants without cardiovascular risk factors was not doable. Discriminating between the effects of several risk factors on vascular disease is therefore only possible for risk factors that are strongly associated with progression of white matter lesions or with a decline of cerebral blood flow.

Participants in this study were all participants of the PROSPER trial [19]. The results of the pharmacological intervention in this MRI study must be seen in light of this study. In our study and in the PROSPER study three years of treatment with pravastatin did not prevent stroke. The PROSPER study had a median follow-up of three years, which is relatively short compared to other statin studies. However, most statin trials in middle-aged men show a stroke reduction within two years of follow-up and the Heart Protection Study in particular showed a stroke reduction already after one year of follow-up.[20] This indicates that three years of follow-up in PROSPER is unlikely to be the main reason for not having a beneficial effect of pravastatin on the prevention of cerebral infarcts. A second explanation for the absence of a clinical effect on stroke may be the age at entry of the PROSPER

study. Participants were aged between 70 and 82 years at entry, which is a relatively old group compared to other trials. Clinical stroke in middle-aged men has a different profile than stroke in the elderly. Before the age of 70 most events of stroke are equally due to ischemic as haemorrhagic causes, but after the age of 70 the incidence of ischemic stroke shows a strong progression. Because of the heterogeneity in causes for stroke, the results of statin trials in middle-aged men like the recently published Sparcl Study and the results in statin trials in the elderly, can not be compared [21]. However, the Heart Protection Study showed a benefit of simvastatin on the primary prevention of stroke in 5806 participants aged 70 years and over. This finding clearly contradicts our findings and the findings in 5804 participants of the PROSPER study. Hence, we think that age per se can not be the main reason why the MRI study and clinical outcome of the PROSPER study showed no beneficial effect of statin use in the prevention of stroke. We consider it more likely that the explanation of the results of our study lies in the history of disease of the participants. Just over 10% of subjects in this MRI study, and therefore also the PROSPER study, had a history of myocardial infarction while over 60% had a history of hypertension. Therefore, subjects in our study were relatively free from coronary heart disease at baseline. These population characteristics are the reverse of those in the Heart Protection Study. Over 60% of subjects in the Heart Protection Study presented with coronary disease while less than 30% had signs of hypertension. We think that this difference in concomitant coronary disease between the two trials is crucial in explaining the difference in outcome with regard to stroke prevention. The high prevalence of coronary heart disease in the Heart Protection Study, combined with the early beneficial effect of statin on stroke prevention, suggests that in the Heart Protection Study mainly cardio-embolic strokes have been prevented. Plaque stabilisation by statins in coronary arteries prevents coronary heart disease associated with transmural ischemic events and or movement disorders of the cardiac wall causing cerebral embolic infarcts [22, 23]. Because of the low prevalence of coronary heart disease in PROSPER, the trial may have been too small to demonstrate a prevention of cardio-embolic strokes. However, when this scenario of insufficient power is at play, we would have expected to find a benefit when measuring cerebrovascular

pathologies on MRI. The results of this MRI study clearly demonstrate that we did not find an argument that statins prevent development or deterioration of cerebrovascular disease, because there were similar progression rates in the total volume of ischemic lesions, white matter hyperintensities, and infarcts in the group treated with pravastatin and the placebo group. These sobering results are in line with the results of the Heart Protection Study, where treatment with simvastatin did not reduce stroke risk in participants with pre-existing cerebrovascular disease. Finally, our results may be influenced by type of statin. However, we found a LDL reduction of 34% after 3 months treatment, which is comparable to other statin trials. Furthermore, several clinical trials have found a benefit of pravastatin on stroke prevention in middle-aged men [16, 17]. Therefore we consider it unlikely that our results only hold for pravastatin and not for statins in general.

Implications

The etiology of cerebrovascular disease is not completely clear yet. In this work we tried to elucidate some of its etiology. Age-related white matter hyperintensities and cerebral infarcts are both indicators of cerebrovascular disease. Prevalence of deep white matter hyperintensities was in our study related to a history of hypertension, and progression of periventricular white matter hyperintensities was related to current smoking. Neuro-anatomical studies suggest that periventricular and deep white matter hyperintensities indeed have a different etiology [5-8]. The development of periventricular white matter hyperintensities has been attributed to arteriosclerosis and lipohyalinosis of the long penetrating arteries in combination with impaired autoregulation which may result in hypoxia of the periventricular white matter [5]. Also, collagenous thickening of the periventricular-draining veins and breakdown of the blood-brain barrier are suggested as mechanisms in the development of periventricular white matter hyperintensities [6, 7]. Deep white matter hyperintensities are thought to be caused by fibrohyalinosis [8].

We found total cerebral blood flow to be associated with progression of periventricular but not deep white matter hyperintensities. Periventricular white matter hyperintensities are typically located symmetrically in both cerebral hemispheres, which is suggestive for a diffuse perfusion disturbance. On the

contrary, deep white matter hyperintensities often are smaller and have an asymmetrical distribution suggesting local perfusion disturbances. The method of total cerebral blood flow measurement in our study is able to detect cerebral blood flow changes based on widespread small-vessel disease [24]. Local cerebral blood flow reductions, such as vascular occlusions caused by small thrombo-embolic events, are less likely to be detected by this method since they will not substantially affect total cerebral blood flow. Our data suggest that periventricular white matter hyperintensities are due to a diffuse perfusion disturbance as measured by a decline in total cerebral blood flow, while deep white matter hyperintensities are not likely due to local perfusion disturbances because of occlusion of a small vessel.

Cerebral infarcts can be categorized as cortical, subcortical and lacunar infarcts [14]. Cortical infarcts are located in the cortical grey matter, where subcortical and lacunar infarcts are located in the white matter and basal ganglia. A lacunar infarct is a specific subcortical infarct and is defined as a small, deep subcortical infarct, due to the occlusion of a small penetrating vessel [9]. The available evidence suggests that cardiac or artery-to-artery embolism from carotid or middle cerebral artery atheroma is the most likely cause of cortical infarcts, while either intracranial atherosclerosis or lipohyalinosis are suggested as underlying vascular pathology of subcortical and lacunar infarcts [9, 10]. In our study we observed that subcortical but not cortical cerebral infarcts are related to white matter hyperintensities. The baseline volume of periventricular white matter hyperintensities predicted the occurrence of a new subcortical infarct during follow-up suggesting that periventricular white matter hyperintensities and subcortical infarcts share, in part, the same etiology: atherosclerosis or lipohyalinosis of the long penetrating arteries.

Future research

The impact of cerebrovascular disease on health of older people necessitates better identification of risk factors and evaluation of preventive and therapeutic strategies. New studies should use techniques which are able to estimate the burden of cerebrovascular disease with good sensitivity and reliability. In our study we investigated the effect of total cerebral blood flow by measuring flow in the supplying vessels of the brain. Although this method permits detection of flow

changes that are due to widespread small vessel disease, it does not reflect flow changes due to focal small vessel changes [24]. Such local changes can be detected by other methods, such as MR perfusion techniques. However, when our studies were performed, MR perfusion techniques still required intravenous administration of gadolinium, which was regarded as too invasive a procedure for our study population [18]. Currently, a new MR perfusion technique, based on arterial spin labelling (ASL), has been developed. This methods permits assessment of regional and total blood flow, without requiring the use of contrast agents, and therefore it qualifies as an ideal technique for studying cerebrovascular changes in population based studies [25].

In this MRI study we suggest that both types of white matter hyperintensities probably have a different etiology. Future studies investigating cerebrovascular disease should take this into account. White matter hyperintensities should be differentiated into a periventricular location and a deep, subcortical location. We argue that periventricular white matter hyperintensities relate to an overall low perfusion of the brain, whereas deep white matter hyperintensities relate to the occlusion of one small vessel. Subtypes of cerebral infarcts have a different etiology too. Together with a new method of measuring cerebral blood flow, future research on the etiology of vascular disease should be able to differentiate between various subtypes of vascular disease in order to learn more about different pathophysiology.

In conclusion, in this MRI study we showed that statins do not have a preventive effect on cerebrovascular disease in the elderly. Future studies on preventing cerebrovascular disease should no longer focus on cholesterol and statin treatment. Besides hypertension treatment and programs for stopping smoking, new methods of intervention should be searched for in the race of lessening the burden of cerebrovascular disease.

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