Vascular factors in dementia: prevention and pathology
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Vascular care in Alzheimer patients with cerebrovascular lesions slows progression of white matter lesions on MRI

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Abstract

**Background and purpose:** White matter lesions (WML) and cerebral infarcts are common findings in Alzheimer’s disease and may contribute to dementia severity. WMLs and lacunar infarcts may provide a potential target for intervention strategies. This study assessed whether multi-component vascular care in Alzheimer’s disease patients with cerebrovascular lesions slows progression of WMLs and prevents occurrence of new infarcts.

**Methods:** A randomized controlled clinical trial, including 123 subjects, compared vascular care with standard care in patients with Alzheimer’s disease with cerebrovascular lesions on MRI. Progression of WMLs, lacunes, medial temporal lobe atrophy and global cortical atrophy were semi-quantitatively scored after 2-year follow-up.

**Results:** Sixty-five subjects (36 vascular care, 29 standard care) had a baseline and a follow-up MRI and in 58 subjects a follow-up scan could not be obtained due to advanced dementia or death. Subjects in the vascular care group had less progression of WMLs as measured with the WML change score (1.4 vs. 2.3, p = 0.03). There was no difference in the number of new lacunes change in global cortical atrophy or medial temporal lobe atrophy between the two groups.

**Conclusions:** Vascular care in patients with Alzheimer’s disease with cerebrovascular lesions slows progression of WMLs. Treatment aimed at vascular risk factors in patients with early Alzheimer’s disease may be beneficial, possibly in an even earlier stage of the disease.
Introduction

Alzheimer’s disease (AD) is a neurodegenerative disease characterized by extracellular deposits of amyloid-beta (Aβ) and intracellular tangles of hyperphosphorylated tau-protein on neuropathology. On MRI, the most important features of AD are medial temporal lobe atrophy (MTLA) and global cortical atrophy (GCA). Cerebrovascular lesions, such as white matter lesions (WML) and (lacunar) infarcts, are common findings on neuro-imaging in cognitively intact elderly and are associated with an increased risk of dementia. Most cases clinically diagnosed as AD often have cerebrovascular lesions as well, and a large number of AD patients, especially the older patients, probably suffer from what can be called ‘mixed dementia’. AD patients with cerebrovascular lesions have fewer plaques and tangles than AD patients without vascular damage, suggesting that cerebrovascular lesions contribute to the dementia syndrome and its severity. This is supported by the finding that the correlation between plaque and tangle load with dementia severity strongly decreases with increasing age, suggesting that other factors contribute to the dementia syndrome. In addition to these radiological and pathological findings, vascular risk factors like hypertension, diabetes, hypercholesterolemia and adiposity have consistently been associated with an increased risk of AD.

Both increase of WML and the occurrence of new lacunar infarcts over time occur in cognitively intact elderly subjects and AD patients. Several vascular risk factors including systolic hypertension, overweight and high triglycerides have been shown to be risk factors for increase of cerebrovascular lesions and progression of WML in AD is correlated to blood pressure. Therapies that aim to improve the cardiovascular risk profile therefore have the potential to decrease the progression of cognitive decline by preventing the occurrence of additional cerebrovascular lesions. Treatment of cardiovascular risk factors reduces the risk of incident and recurrent stroke and treatment of hypertension reduces the risk of incident dementia, including AD. Whether treatment of other cardiovascular risk factors (e.g. hypercholesterolemia, hyperhomocysteinemia and lack of physical exercise) can prevent additional WML and lacunar infarcts, and via this pathway progression of cognitive decline, is currently uncertain.

The aim of this study is to evaluate whether a multi component intervention strategy aimed at various vascular risk factors in early AD patients with cerebrovascular lesions can prevent additional WML and cerebral infarcts, in order to slow down disease progression.
# Methods

## Study population

The patients for this study were participating in the EVA-study (Evaluation of Vascular care in Alzheimer’s disease), a multi-centre randomized controlled clinical trial in 123 patients investigating whether vascular care could slow down dementia progression.\(^{17}\) Inclusion criteria were age over 65 years, fulfilling the clinical criteria for the diagnosis ‘probable AD’,\(^{18}\) judged to be mild as based on global clinical judgement, and the presence of cerebrovascular lesions on MRI. Patients with WML of presumed vascular origin or (lacunar) infarcts were eligible. Exclusion criteria were epilepsy, focal neurological deficits other than cognitive deficits or any condition that would preclude a follow up of 24 months. Recruitment of patients took place between October 2002 and May 2005. The study was performed in ten participating hospitals, including three academic hospitals, five large teaching hospitals and two mid-size community hospitals. The study was approved by the medical ethical committees of all 10 participating hospitals and all patients or their legal representative gave written informed consent.

## Study design and interventions

The study was designed as a randomized controlled trial comparing a multi component intervention strategy aimed at various vascular risk factors, referred to as vascular care (VC) to standard care (SC). Randomization took place according to a computer generated code in a 1:1 ratio in randomized permuted blocks of 4. The intervention group received vascular care consisting of a combination of lifestyle interventions (weight loss and dietary advice in case of a BMI > 25 kg/m², physical exercise, smoking cessation) and medication (acetylsalicylic acid 38-100 mg, pyridoxine 50 mg and folic acid 0.5 mg). Hypertension was treated according to a stepped protocol, starting with reducing salt intake and increasing exercise, followed by a diuretic, and if necessary addition of a beta-blocker or a calcium antagonist. in case of a systolic pressure > 140 mm Hg or a diastolic pressure > 90 mm Hg. Hypercholesterolemia was treated with pravastatin 40 mg in case of a total cholesterol > 5 mmol/l and in case of a high glucose or glucose intolerance an internist was consulted. For the VC patients follow-up visits were scheduled every three months to monitor adherence to the treatment protocol and adjust both the medical and the non-medical interventions when necessary in a tailor-made way for each patient. The SC patients were referred back to their general physician (GP). Follow-up was at one year and at two years for clinical parameters and a follow-up MRI was obtained at two year follow-up.

## Outcome parameters

The primary outcome parameter of this study was the progression of white matter lesions and the occurrence of new lacunar infarcts. Secondary outcome parameters were progression of GCA and MTLA and the occurrence of new cortical infarcts.
**MRI examination**

The MRI-scans at baseline and at follow-up were obtained in the hospital where the patient was included and where the follow-up was done. Except for one patient, baseline and follow-up scan were on the same machine. MRI-scanners were 1.5T machines of various vendors. One centre used a 1.0T scanner. The scanning protocol was uniform for all centres and included the following sequences: Axial FLAIR (fluid-attenuated inversion recovery), T1-weighted 3D MPRAGE (magnetization prepared rapid-acquisition gradient-echo) in the coronal or sagittal plane with coronal reconstruction, T2-Fast Spin Echo in the axial or coronal plain. A small proportion of the baseline scans (25.4%) were only available on film. The rest of the baseline scans and all the follow-up scans were uploaded on a single workstation and analyzed by a single, trained rater (ER), who was blind to the clinical data and treatment allocation.

WML at baseline were visually rated on the axial FLAIR with the use of two semi-quantitative rating scales. The Fazekas scale is a four-point scale (none, mild, moderate, severe) rating the extent and severity of the deep white matter changes and the Scheltens scale, a scale in which WML are rated 0-6 in 13 subcortical regions including the basal ganglia and infratentorial region, and 0-2 in 3 periventricular regions, resulting in a total range of 0-84.\(^\text{19, 20}\) Progression of WML was rated with the use of the modified WML change score, in which WML progression can be scored as decrease, stable or increase in four subcortical regions (frontal, parietal, temporal, occipital), three periventricular regions (frontal caps, occipital caps, lateral bands), basal ganglia and infratentorial, thus leading to a change-score of zero to nine (theoretically the minimum score is minus 9, but decrease of WML did not occur in our sample).\(^\text{21}\) For this rating scale the two scans were rated side-by-side.

The number of lacunes (defined as round or ovoid cavities of 3-10 mm) and larger subcortical or cortical infarcts was counted at baseline and follow-up with the use of the FLAIR, MPRAGE and T2-weighted images. GCA was rated on the axial FLAIR using a 4-point visual rating scale (1 = none, 2 = widening of sulci, 3 = atrophy of gyri, 4= end stage atrophy with ‘razor-blade’ gyri).\(^\text{22}\) MTLA was visually rated on coronal MPRAGE when available, and coronal FLAIR in the other cases using a 5-point scale (0 = none, 1 = widening of Choroid fissure, 2 = widening temporal horn, opening fusiform and collateral sulcus, 3 = profound volume loss hippocampus, 4 = end stage atrophy).\(^\text{23}\) The mean of the left and right MTLA score was used in the analysis. For calculating MTLA and GCA progression and occurrence of new lacunar infarcts, change scores were calculated by subtracting baseline score from follow-up score. The intrarater reliability for semiquantitative rating of WML, MTLA and GCA was determined on a standardized set of 20 scans at the image analysis center of VU University Medical Center. Cohen’s kappa was > 0.9 for WML (for both the Fazekas and Scheltens scales), 0.9 for GCA and 0.8 for MTA.
Statistical analysis

Group differences at baseline were assessed using student’s T-tests for normally distributed continuous variables, Mann-Whitney U tests for continuous not normally distributed variables or ordinal variables and Chi-square or Fisher Exact statistics for dichotomous variables.

The modified WML change score was analyzed using Mann-Whitney-U statistics. In addition it was trichotomized into none, medium (1-3 points), severe (> 3 points) and analyzed with Chi-square statistics with linear by linear association. To correct for the difference in diastolic blood pressure between the groups at baseline, an ordinal regression model was used with diastolic blood pressure as a covariate. To correct for baseline WML severity, an ordinal regression model was used with baseline Scheltens score as a covariate. The occurrence of new lacunes and cortical infarcts was analyzed with Mann-Whitney-U and Chi-square statistics. Progression of MTLA was analyzed using Chi-square statistics, where MTLA was dichotomized in any progression versus no progression and GCA was analyzed with Mann-Whitney U statistics. All analyses were done using SPSS 15 for Windows.

Results

Sample characteristics

Of 123 patients in the EVA-trial, a follow-up MRI could be obtained in 65 (29 (51%) in the SC group vs. 36 (55%) in the VC group, p = 0.62). No follow-up MRI could be obtained in 58 patients because of death (n = 11; 6 in the SC group, 5 in the VC group), care-giver burden or institutionalization in a condition that precluded follow-up. Patients who did not have a follow-up scan had more advanced dementia at baseline as reflected in lower scores on the MMSE (21.4 [SD 3.5] vs. 23.0 [SD 3.3], p = 0.01). They also had more severe WML as measured both with the Fazekas scale (2.26 [SD 0.8] vs. 1.89 [SD 0.8], p = 0.01) and with the Scheltens scale (21.75 [SD 7.7] vs. 18.00 [SD 7.3], p = 0.008). There were no differences in lacunes, cortical infarcts, GCA, MTLA, demographic characteristics, bloodpressure (BP), or laboratory parameters between the group with and without follow-up scan.

The baseline characteristics of 65 subjects with follow-up scan included in this MRI-analysis are shown in Table 1. Except for a higher diastolic BP in the SC group (88.0 vs. 80.8, p = 0.02), there were no differences at baseline. At follow-up not all sequences could be obtained in every patient. For this reason the progression of abnormalities could not be reliably scored in some patients (3 for WML, 13 for MTLA, 1 for GCA, 4 for lacunes).
Progression of MRI parameters

Figure 1 shows the distribution of the WML change score between the VC and SC groups. Over a 2 year follow-up period, the VC group had less WML progression: 1.4 (SD 1.63) points on the modified WML change score, as compared to 2.3 (SD 1.63) in the SC group (table 2). This 38% difference was statistically significant (p = 0.03) and the linear by linear association showed a significant linear trend (p=0.009). When using diastolic blood pressure as a covariate in an ordinal regression model, this did not change the effect of the intervention (p = 0.02). No correlation was found between baseline severity of WML (both with Fazekas score and Scheltens score) and modified WML change score in the intervention group (Spearman’s rho -0.07, p = 0.70) and when baseline Scheltens score was used as a covariate in an ordinal regression model the difference in modified WML change score remained significant (p = 0.03).

Progression of MTLA, GCA and occurrence of new lacunes is listed in table 2. There was no difference between the number of patients with new lacunes in the SC and the VC group (7 (25%) vs. 5 (15.2%), p = 0.34). Of the patients with new lacunes, six had already lacunes at baseline (3 in SC group and 3 in VC group). No difference between groups was found with respect to new cortical infarcts, MTLA progression or GCA progression. (table 2)

Discussion

This study shows that a multi-component intervention aimed at several vascular risk factors, including both medical and non-medical interventions, leads to less WML.
Chapter 3

Table 1. Baseline parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard care N = 29</th>
<th>Vascular care N = 36</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>75.3 (3.9)</td>
<td>76.8 (5.7)</td>
<td>0.24</td>
</tr>
<tr>
<td>Sex; female, n (%)</td>
<td>16 (55.2)</td>
<td>18 (50.0)</td>
<td>0.44</td>
</tr>
<tr>
<td>Bloodpressure</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Systolic, mmHg</td>
<td>159.7 (23.7)</td>
<td>151.0 (24.8)</td>
<td>0.15</td>
</tr>
<tr>
<td>Diastolic, mmHg</td>
<td>88.0 (13.5)</td>
<td>80.8 (10.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>MMSE</td>
<td>22.8 (3.2)</td>
<td>23.2 (3.4)</td>
<td>0.66</td>
</tr>
<tr>
<td>Radiological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WML Fazekas n (%)</td>
<td>0 (0.0)</td>
<td>1 (2.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (31.0)</td>
<td>13 (36.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (31.0)</td>
<td>16 (44.4)</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>3 (37.9)</td>
<td>6 (16.7)</td>
<td></td>
</tr>
<tr>
<td>WML Scheltens, mean (SD)</td>
<td>18.9 (6.5)</td>
<td>17.2 (7.9)</td>
<td>0.36</td>
</tr>
<tr>
<td>GCA, n (%)</td>
<td>0 (6.9)</td>
<td>3 (8.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (55.2)</td>
<td>21 (60.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (34.5)</td>
<td>10 (28.6)</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>3 (3.4)</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td>MTLA, mean (SD)</td>
<td>1.7 (0.9)</td>
<td>1.6 (0.8)</td>
<td>0.48</td>
</tr>
<tr>
<td>Lacunes, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 (65.5)</td>
<td>26 (72.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-3 (31.0)</td>
<td>8 (22.2)</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>&gt;3 (3.4)</td>
<td>2 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Cortical infarct, n(%)</td>
<td>2 (6.9)</td>
<td>2 (5.6)</td>
<td></td>
</tr>
</tbody>
</table>

MMSE: Mini Mental State Examination, WML: white matter lesions, SD: standard deviation, GCA: global cortical atrophy, MTLA: medial temporal lobe atrophy.

Table 2. MRI progression of abnormalities

<table>
<thead>
<tr>
<th></th>
<th>Standard care (n=29)</th>
<th>Vascular care (n=36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>WML change (SD)</td>
<td>2.29 (1.63)</td>
<td>1.41 (1.33)</td>
<td>0.03</td>
</tr>
<tr>
<td>New lacunes, n (%)</td>
<td>7 (25.0)</td>
<td>5 (15.2)</td>
<td>0.26</td>
</tr>
<tr>
<td>MTLA progression n (%)</td>
<td>19 (65.5)</td>
<td>25 (69.4)</td>
<td>0.79</td>
</tr>
<tr>
<td>GCA progressionn (%)</td>
<td>6 (21.4)</td>
<td>10 (31.3)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

WML change: White Matter Lesion change score, MTLA: Medial Temporal Lobe Atrophy, GCA: Global Cortical Atrophy.
progression in AD patients with cerebrovascular lesions. This effect on the progression of WML could potentially influence cognitive decline since cerebrovascular lesions in AD patients contribute to the severity of cognitive decline.\textsuperscript{7, 8} However, in this population this did not lead to clinical benefit, as we described before.\textsuperscript{17} The reason for this lack of a clinical effect could be that the disease was already too advanced in this group. Although the dementia severity was certainly mild in our sample, it is well-known that the neuropathological changes underlying the dementia predate the clinical occurrence of dementia.\textsuperscript{24} In addition the WML were already moderately severe in our sample with an average Scheltens score of 18 points. Starting a multi-component intervention aimed at vascular risk factors earlier, in non-demented elderly subjects, might slow down progression (or occurrence) of WML in a similar way, and help to preserve cognition in elderly subjects.\textsuperscript{25}

In this study, we did not find a difference in the occurrence of new lacunes between groups. However, the small number of lacunes (and larger infarcts) both at baseline and at follow-up precludes a conclusion about the effect of the intervention on the occurrence of new lacunes and larger infarcts if multi-component vascular care would be implemented on a large scale. Moreover, vascular care had no influence on the progression of both GCA and MTLA. Although these parameters were not the primary endpoint of this study and the study was not powered to detect differences on these parameters, analysis was considered appropriate, because both hippocampal atrophy and cortical atrophy have been found to be associated with elevated blood pressure.\textsuperscript{26, 27} The population in this study is a selection, because not in all patients included in the trial an MRI could be obtained after 2 years due to the progressive nature of the disease and the relatively long follow-up for an AD intervention-trial. This selection does however not influence the interpretation of the findings, since the patients available for MRI-analysis were well balanced between the SC and VC groups.

We used visual rating scales, and no volumetric measurements. The accuracy and intrarater agreement of visual semi-quantitative rating of WML is comparably accurate to quantitative measurements, and therefore no limitation to our study results.\textsuperscript{28, 29} The higher diastolic blood pressure in the SC group could have been a confounder, masking the result of our intervention, since higher blood pressure, particularly diastolic, is associated with more WML progression, making the SC group prone to more progression of WML.\textsuperscript{13} But when using the diastolic blood pressure as a covariate, the effect of the intervention did not change. Although progression of WML is correlated with WML severity at baseline\textsuperscript{12}, we did not find a correlation between baseline severity and effect of the intervention. The results of this study are encouraging for designing intervention trials aimed at several vascular risk factors at an earlier stage, in subjects who are not demented yet. Such trials would have to be very large with a long follow-up and at least one large clinical trial addressing the question whether multi-component vascular care can prevent dementia in non-demented elderly is underway.\textsuperscript{30}
Reference List


