Vascular factors in dementia: prevention and pathology
Richard, E.

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Chapter 2

Vascular care in Alzheimer patients with cerebrovascular lesions – a randomized clinical trial

E. Richard
R. Kuiper
M.G.W. Dijkgraaf
W.A. Van Gool

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Abstract

**Objectives:** To investigate whether vascular care slows dementia progression in Alzheimer patients with cerebrovascular lesions on neuroimaging.

**Design:** Multicenter randomized controlled clinical trial with two year follow-up.

**Setting:** Neurological and geriatric outpatient clinics in ten Dutch hospitals: three academic, five teaching and two midsize community hospitals.

**Participants:** One hundred thirty community-dwelling patients with mild dementia fulfilling clinical criteria for Alzheimer’s disease with cerebrovascular lesions on neuroimaging.

**Intervention:** Patients randomized to *vascular care* were treated according to strict guidelines for hypercholesterolemia and hypertension. Acetylsalicylic acid, folic acid and pyridoxine were prescribed. During visits every three months special attention was paid to smoking cessation, losing weight and stimulating physical exercise.

**Measurements:** Primary outcome was disability, measured according to the Interview for Deterioration in Daily activities in Dementia (IDDD). Secondary outcomes were changes on the Mini Mental State Examination (MMSE), the Revised Memory and Behavioural Problems Checklist (RMBPC), a composite measure of ‘poor outcome’ (death, institutionalization or severe clinical decline), and costs.

**Results:** Patients in the vascular and standard care condition declined equally on the IDDD (13.7 point vs. 11.0; difference 2.71; 95%CI: -3.1;8.6). There was no treatment effect on the MMSE and RMBPC. There were no differences in institutionalization rate, ‘poor outcome’ (58.6% vs. 58.5%, \( p = 0.61 \)) or costs. In the intervention group there were three intracerebral haemorrhages and one gastro-intestinal haemorrhage, versus none in the control group.

**Conclusions:** Multi-component vascular care, combining pharmacological and non-pharmacological interventions, does not slow decline in Alzheimer patients with cerebrovascular lesions.
Introduction

Several lines of evidence suggest that in many patients with dementia the previous sharp distinction between a neurodegenerative and a vascular cause may not longer be tenable.\textsuperscript{1,2} Epidemiological studies have consistently documented associations between vascular risk factors and Alzheimer’s disease (AD).\textsuperscript{3} Hypertension, diabetes and hyperhomocysteiminia in the elderly have all been associated with an increased risk of dementia.\textsuperscript{4-6} Similar associations have been described for smoking, lack of physical exercise, obesity and (midlife) hypercholesterolemia.\textsuperscript{7-10} In addition, in elderly people, the ‘metabolic syndrome’, consisting of several of these individual risk factors taken together, has been associated with an increased risk for AD.\textsuperscript{11} Moreover, autopsy studies show that a large proportion of patients fulfilling clinical criteria for AD have mixed pathology, with both cerebrovascular lesions as well as plaques and tangles.\textsuperscript{12} Clinico-pathological studies show that patients clinically diagnosed with AD with cerebrovascular lesions have fewer plaques and tangles than patients without, strongly suggesting a contribution of the cerebrovascular lesions to the clinical dementia syndrome.\textsuperscript{13,14} Consistent with these pathological observations, neuroradiological examinations show that cerebral white matter lesions and clinically silent infarcts increase the risk of future dementia.\textsuperscript{15,16}

Whereas the neurodegenerative component of AD is not amenable to treatment as yet, the vascular risk factors may represent a therapeutic target. The use of antihypertensive drugs has been associated with a lower incidence of dementia,\textsuperscript{17} and treatment of hypertension has been shown to reduce incident dementia in randomized clinical trials.\textsuperscript{18} Studies on the effect of lowering homocysteine and cholesterol have yielded inconsistent results\textsuperscript{19-22}, and a recently published randomized controlled trial found no effect on cognitive decline of the use of B-vitamins alone.\textsuperscript{23} Although physical exercise has been associated with a decreased risk of dementia, no data are available on life-style interventions in late life.\textsuperscript{24} Acetylsalicylic acid use has been associated with a lower risk for AD, but a recent open-label intervention study could not confirm this effect\textsuperscript{25,26} and it’s role in vascular dementia is unclear.\textsuperscript{27} Several authors, some more than 15 years ago, have recognized the need for clinical studies on the vascular component of dementia\textsuperscript{28} yet no study has ever addressed the question whether treatment of vascular risk factors in early AD patients with cerebrovascular lesions can actually slow down dementia progression. It was hypothesized that preventing additional cerebrovascular lesions would result in less cognitive decline. The synergistic effect of AD pathology and cerebral infarcts on cognition makes the effect of such an intervention plausible. A randomized clinical study was designed to investigate whether a multi-component intervention aimed at many vascular risk factors could result in clinical benefit for AD patients.
Methods

Study design and objectives
The study was designed as a multicenter randomized controlled trial comparing standard care (SC) to vascular care (VC), with assessment of clinical outcomes. Randomization was done centrally according to a computer generated code in a 1:1 ratio in randomized permuted blocks of 4. The medical ethical committees of all 10 participating hospitals approved the study. All patients and their legal representative gave written informed consent. The objective of the study was to investigate whether VC in AD patients with cerebrovascular lesions could slow down disease progression over 24 months as measured by clinical outcome parameters.

Patients
Patients were recruited through memory outpatient clinics of participating hospitals (three academic hospitals, five large teaching hospitals and two mid-size community hospitals). The inclusion criteria were aged 65 and older and fulfilling clinical criteria for the diagnosis ‘probable Alzheimer’s disease’29, with minimal or mild severity according to the guidelines for gradation of dementia in the ‘Cambridge Examination for Mental Disorders in the Elderly schedule’ (CAMDEX).30 White matter lesions of vascular of origin31 or one or more infarcts (lacunar or cortical) on MRI had to be present. A caregiver had to be available to assure adherence to therapy and to complete questionnaires (see below). Exclusion criteria were epilepsy, focal neurological deficits other than cognitive deficits or any condition that would preclude a follow up of 24 months.

At baseline all patients underwent neurological examination. Medical history and medication use were registered and blood pressure, weight and smoking habits were recorded. Blood was drawn for analysis of glucose, hemoglobin A1c, homocysteine, vitamin B12, folic acid, lipid-profile and creatinine. All patients underwent the same analyses again after 1 and after 2 years.

Intervention
The treating neurologist or geriatrician provided VC, which consisted of visits to the outpatient clinic every three months, where patients were treated according to a standardized protocol aimed at reducing the risk for additional cerebrovascular damage. Each patient received acetylsalicylic acid 38-100 mg, pyridoxine 50 mg and folic acid 0.5 mg per day. In case of total blood cholesterol above 5.0 mmol/l pravastatin 40 mg was started. In case of hypertension (systolic pressure exceeding 140 mm Hg or diastolic pressure exceeding 90 mm Hg) antihypertensive treatment was started according to a standardized stepped protocol, starting with reducing salt intake and stimulating exercise, followed by a diuretic, and if necessary addition of a beta-blocker and a calcium-antagonist. Patients with high serum glucose levels or glucose
intolerance were referred to an internist. Smoking cessation was encouraged, and in
overweight patients attention was paid to dietary habits and stimulation of physical
exercise.

Patients allocated to the SC condition were required only to attend the scheduled 1 and
2 year follow-up visits. No specifications were made concerning vascular care in the SC
condition, so patients specialists or GPs treated them according to general guidelines
for treatment of vascular risk factors in the elderly. It was left to the discretion of the
participating physician to schedule extra visits if required as regular care for dementia
patients. Use of acetylcholinesterase-inhibitors (AChEI) was allowed in both treatment
arms.

**Outcome parameters**

Primary outcome measure was the decline in functioning measured according to
activities of daily living (ADL). The Interview for Deterioration in Daily activities in
Dementia (IDDD) is a paper and pencil questionnaire, to be completed by the caregiver
with 11 items and a total score ranging from 0 (ADL independent) to 44 (completely
dependent).

Secondary outcome parameters included the Mini Mental State Examination (MMSE),
a commonly used 11-item cognitive scale ranging from 0-30 points that assesses
multiple domains of cognitive functioning and the Revised Memory and Behavioural
Problems Checklist (RMBPC), a 25-item paper and pencil questionnaire for assessment
of behavioural problems ranging from 0 (no behavioural problems) to 100 (severe
behavioural problems). For missing items on the IDDD and RMBPC, weighted sum
scores based on the actual number of items scored were used.

Attrition due to death or disease progression tends to inflate clinical outcome measures
in trials with a long follow-up of patients with a progressive disease as AD. To overcome
such bias, a binary outcome (‘poor’ vs. ‘not-poor’) was also used, in which ‘poor
outcome’ was defined as death, institutionalization, or deterioration of 1 standard
deviation (SD) or more on at least 2 of the 3 scales (IDDD, MMSE, RMBPC) after two
years. Institutionalization was defined as admission to a nursing home or continuous
nursing care at home. Another secondary outcome measure was costs.

**Statistical analysis**

Based on previous research, disease progression as measured with the primary
outcome was estimated to be 14 to 15 IDDD-points over 2 years, with a SD of about
8 points. With alpha set at .05, the study was designed to have 80% power to detect
slowing of the course of dementia with 4-5 IDDD-points, equivalent to approximately
0.6 SD (corresponding to slowing the course of the disease with 6-7 months over the
study-period). This would require enrolment of about 100 patients; accounting for a
drop-out rate of 20-25%, 130 patients were scheduled to be randomized.
The statistical analysis plan was finalized and potential confounders were pre-specified for use as covariates before the database was locked. Group differences at baseline were assessed using independent sample t-test, Mann-Whitney test and chi-square test or Fisher exact test, where appropriate. General linear models were used for the primary efficacy analysis, with scores for the IDDD, MMSE and RMBPC as the dependent variable, treatment condition as factor and baseline score for the specific measure under study, age, AChEI use and acetylsalicylic acid or coumarin use as covariates. The covariates were selected because of their potential influence on dementia progression over 2 years. Acetylsalicylic acid or coumarin use was included in the model because of imbalance between the two groups at baseline, whereas at the same time this was part of the intervention. Furthermore, whether VC affected body mass index and levels of blood pressure was studied using linear regression models, adjusting for their respective baseline values, age and AChEI use. For the effect on laboratory measures, age and baseline value of the parameter analyzed were adjusted for. These analyses included only patients completing the final assessment at study end (observed-cases), avoiding the need to perform imputations of missing values. A repeated measures analysis on the primary outcome was performed to study potential differences between the treatment conditions in pattern of deterioration. An intention-to-treat analysis of the binary outcome ‘poor vs. not poor’ was performed using a logistic regression model adjusting for age, AChEI use, acetylsalicylic acid or coumarin use and baseline IDDD score. All statistical testing was two-tailed and performed with SPSS 14.0 (SPSS Inc., Chicago, IL).

Cost-effectiveness analysis
A cost-effectiveness analysis (CEA) was performed from a societal perspective with the costs per patient without poor outcome at two years as the primary outcome parameter. Relevant direct medical (study medication, hospital care, institutional care, home care) and non-medical (informal care, out-of-pocket expenses) costs were included. Considering the age of the study population the indirect non-medical costs of production loss at work were discarded. Unit costing for base year 2007 was performed in accordance with standard guidelines for health care research and pharmaceutical guidelines in The Netherlands, resulting in the application of real costs for health care components and market prices for drugs, including a standard pharmacy prescription revenue per drug per quarter. Costs were expressed in Euros. With a 2 year follow-up period and in accordance with current guidelines, costs were also discounted at a rate of 4%. Differences between groups were assessed by calculating 95% confidence intervals for the mean differences after correction for bias and using accelerated non-parametric bootstrapping, drawing 10,000 samples of the same size as the original sample separately for each group and with replacement.
Results

Sample characteristics
Inclusion of the 130 patients took place between November 2002 and April 2005. A flow chart of the trial is presented in figure 1. A total of 94 patients (72.3%) completed the 2-year follow-up. At baseline there were no significant group differences, except that patients in the VC group used acetylsalicylic acid or coumarin derivates more frequently. (Table 1)

Seven patients were excluded from the study and all subsequent analyses because they withdrew consent before the baseline assessment (5), or the inclusion criteria were violated (2). The drop-out rate was similar in both groups. Most drop-outs were the result of dementia progression, caregiver burden, or institutionalization in a condition that precluded outpatient-clinic visits. To minimize drop-out, trial nurses visited

![Flowchart of the study.](image-url)
Table 1. Baseline demographic, laboratory and clinical characteristics

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Standard care (n=58)</th>
<th>Vascular care (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>76.2 (4.8)</td>
<td>76.7 (5.6)</td>
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<tr>
<td>Disease duration, y (SD)</td>
<td>2.3 (1.5)</td>
<td>2.5 (1.5)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>35 (60.3)</td>
<td>35 (53.8)</td>
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<tr>
<td>Male</td>
<td>23 (39.7)</td>
<td>30 (46.2)</td>
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<tr>
<td>Education</td>
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<td></td>
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<tr>
<td>&lt; 7 years</td>
<td>14 (24.1)</td>
<td>15 (23.1)</td>
</tr>
<tr>
<td>7-11 years</td>
<td>34 (58.6)</td>
<td>41 (63.1)</td>
</tr>
<tr>
<td>&gt; 11 years</td>
<td>7 (12.1)</td>
<td>9 (13.8)</td>
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<tr>
<td>Unknown</td>
<td>3 (5.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 unit/week</td>
<td>26 (44.8)</td>
<td>34 (52.3)</td>
</tr>
<tr>
<td>&lt;1 unit/day &gt;1 unit/week</td>
<td>8 (13.8)</td>
<td>12 (18.5)</td>
</tr>
<tr>
<td>&gt;1 unit/day</td>
<td>23 (39.7)</td>
<td>18 (27.7)</td>
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<td>Unknown</td>
<td>1 (1.7)</td>
<td>1 (1.5)</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Current</td>
<td>5 (8.6)</td>
<td>3 (4.6)</td>
</tr>
<tr>
<td>Ever</td>
<td>31 (53.4)</td>
<td>26 (40.0)</td>
</tr>
<tr>
<td>Never</td>
<td>22 (37.9)</td>
<td>36 (55.4)</td>
</tr>
<tr>
<td>Drug use:</td>
<td></td>
<td></td>
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<tr>
<td>Cholinesterase inhibitor/memantine</td>
<td>18 (31.0)</td>
<td>21 (32.3)</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>24 (41.4)</td>
<td>31 (47.7)</td>
</tr>
<tr>
<td>Acetylsalicylic acid/coumarin</td>
<td>16 (27.6)</td>
<td>29 (44.6)</td>
</tr>
<tr>
<td>Lipid-lowering drug</td>
<td>13 (22.4)</td>
<td>10 (15.4)</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>6 (10.3)</td>
<td>3 (4.6)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>8 (13.8)</td>
<td>12 (18.5)</td>
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Physical and laboratory characteristics

<table>
<thead>
<tr>
<th>Blood pressure</th>
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<tbody>
<tr>
<td>Systolic, mmHg</td>
<td>156.1 (24.5)</td>
<td>153.6 (22.6)</td>
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<tr>
<td>Diastolic, mmHg</td>
<td>86.2 (12.5)</td>
<td>82.7 (9.5)</td>
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<tr>
<td>Weight, kg</td>
<td>74.1 (13.8)</td>
<td>73.5 (12.5)</td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>26.3 (4.3)</td>
<td>26.0 (4.3)</td>
</tr>
<tr>
<td>Blood values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>5.8 (1.3)</td>
<td>5.7 (1.2)</td>
</tr>
<tr>
<td>HbA1C, %</td>
<td>5.9 (0.7)</td>
<td>5.9 (0.6)</td>
</tr>
<tr>
<td>Homocysteine, μmol/l</td>
<td>14.6 (5.9)</td>
<td>16.3 (10.4)</td>
</tr>
<tr>
<td>Folic Acid, nmol/l</td>
<td>17.4 (9.1)</td>
<td>18.4 (12.2)</td>
</tr>
<tr>
<td>Vitamine B12, pmol/l</td>
<td>310.7 (139.9)</td>
<td>309.3 (160.5)</td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>1.5 (1.0)</td>
<td>1.6 (0.8)</td>
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Table 1. cont.

<table>
<thead>
<tr>
<th>Physical and laboratory characteristics</th>
<th>Standard care (n=58)</th>
<th>Vascular care (n=65)</th>
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<tbody>
<tr>
<td>Tot cholesterol, mmol/l</td>
<td>5.6 (1.2)</td>
<td>5.8 (1.2)</td>
</tr>
<tr>
<td>HDL, mmol/l</td>
<td>1.7 (0.5)</td>
<td>1.6 (0.5)</td>
</tr>
<tr>
<td>LDL, mmol/l</td>
<td>3.4 (1.0)</td>
<td>3.6 (1.1)</td>
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Clinical scores

<table>
<thead>
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<th>Standard care (n=58)</th>
<th>Vascular care (n=65)</th>
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<tbody>
<tr>
<td>Interview for Deterioration of Daily activities in Dementia</td>
<td>10.7 (9.3)</td>
<td>9.5 (9.4)</td>
</tr>
<tr>
<td>Mini Mental Status Examination</td>
<td>22.2 (3.6)</td>
<td>22.3 (3.3)</td>
</tr>
<tr>
<td>Revised Memory and Behavioural Problems Checklist</td>
<td>26.1 (9.9)</td>
<td>25.5 (10.3)</td>
</tr>
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</table>

MRI abnormalities

<table>
<thead>
<tr>
<th></th>
<th>Standard care (n=58)</th>
<th>Vascular care (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Matter Lesions (Fazekas score)</td>
<td>2.04 (0.80)</td>
<td>2.09 (0.86)</td>
</tr>
<tr>
<td>Lacunes (n, %)</td>
<td>21 (36.8)</td>
<td>20 (31.3)</td>
</tr>
<tr>
<td>Cortical infarct (n, %)</td>
<td>5 (8.8)</td>
<td>8 (12.5)</td>
</tr>
</tbody>
</table>

*No significant group differences were observed, except for acetylsalicylic acid/coumarin use (*p* = 0.05). Values are expressed as number (percentage) unless indicated otherwise. Values are expressed as mean (SD). The Fazekas scale is a semi-quantitative rating scale ranging from 0-3 (none-mild-moderate-severe) and reflects WML severity.29

Figure 2. Clinical outcome measures. Progression on the three clinimetrical scales over 2 years. (A) IDDD: Interview for Deterioration of Daily activities in Dementia (range 0-44). (B) MMSE: Mini Mental Status Examination (range 0-30). RMBPC: (C) Revised Memory and Behavioral Problems Checklist (range 0-100). Vertical bars represent standard error of the mean (SE).

institutionalized patients for completion of follow-up and information about personal situation after 2 years (living at home, institutionalized or dead) could be retrieved in all 123 patients.

Clinical outcomes

There was no significant difference between the two groups in the primary outcome (IDDD) or the secondary outcomes (MMSE and RMBPC) (table 2 and fig. 2). Adjustments for the respective baseline score, age, AChEI-use and acetylsalicylic acid or coumarin-use did not affect this conclusion. A repeated-measures analysis was performed, including the data obtained after 1 year, but this did not affect the results. There were no differences in institutionalization rates (41.4% vs. 35.4%, *p* = 0.50) or
deaths (10.3% vs. 9.2%, $p = 0.84$). A ‘poor outcome’ (death, institutionalization or severe clinical deterioration) occurred in 58.6% in the control group and 58.5% in the VC group ($p = 0.61$, table 3).

**Laboratory outcomes**

Total cholesterol, Low-density lipoprotein cholesterol and homocysteine decreased and folic acid increased significantly in the VC group during follow-up (table 2). Systolic and diastolic blood pressure, calculated as the change over time in each individual patient, decreased significantly in both groups over the two years, without a significant difference between the two treatment strategies (table 2).

**Adverse events and deaths**

Intracerebral hematoma (ICH) caused three of the deaths in the VC group and none in the control group (difference 4.6% (CI -0.5%; 9.7%)); the cause of death of two patients in the SC group was uncertain, but both patients died acutely making an ICH far less
likely than a cardiac cause. The only reported side effects were a gastro-intestinal haemorrhage in one patient and epistaxis in two, all three in the VC group.

**Costs**

During the 2-year follow-up the total undiscounted health care costs per patient were 41,729 euro in the VC group compared with 39,702 euro in the SC group (difference 2,026 euro, 95% CI: minus 11,688 to 15,587). Institutionalization, home care, informal care, and out-of-pocket expenses generated the vast majority of the costs (92% and 95.2% respectively). The extra VC costs of study medication, laboratory analysis, and additional outpatient visits accounted for only 3.4% of the total VC associated costs (1,421 euro). Without better clinical and economic outcomes, the probability of VC being cost-effective compared to SC is low (0.44 at maximum for willingness-to-pay values per prevented poor outcome up to 100,000 euro). Discounting costs hardly changed the results.
Chapter 2

Discussion

The present findings do not support the hypothesis that an intervention aimed at the vascular component of dementia slows disease progression in patients with a clinical diagnosis of early AD with concomitant cerebrovascular lesions. In spite of all epidemiological and pathological evidence of the relevance of vascular factors in AD, no benefit was found in daily functioning, cognitive deficits, or behavioural abnormalities as a result of VC. Because of the multi-component character of the present intervention, the possibility that a beneficial effect of one component of the intervention has outweighed a negative effect of another cannot be excluded. Also, the small sample size of the study renders this conclusion prone to a type II error (i.e. a minute benefit as a result of VC may have been missed), although the follow up period of 2 years, which is relatively long for this type of study, and the use of three dimensions of dementia severity that were probed, should have allowed for any clinically relevant treatment effect to be detected. Moreover, analysis of the trial results with a global outcome, which allowed all patients who died and all retrieved drop-outs to be included, failed to show any benefit of VC in averting an overall ‘poor’ outcome. Close inspection of the data does not suggest even a trend for benefit of VC, but rather the reverse (fig 2).

The study was designed as a randomized controlled open study, because of the nature of the intervention and impossibility of blinding for individualized vascular interventions. Assessment at follow-up by a physician blinded to the treatment allocation would have been difficult, because it was clear to patient and caregiver in which treatment arm the patient was, making appropriate concealment from the physician unlikely, and to the caretaker, who completed the IDDD and RMBPC, impossible. It is likely that any bias resulting from unblinded assessment by the caregiver who completed the IDDD and the RMBPC, or the clinician assessing other parameters, could have expected to favour VC, which was not observed. The power analysis was based on data from regular AD trials, because no specific data on AD patients with cerebrovascular lesions on MRI

Table 3. Binary outcome ‘poor’ vs. ‘not poor’

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Standard care n = 58</th>
<th>Vascular care n = 65</th>
<th>Odds ratio</th>
<th>95 % CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal situation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>living at home</td>
<td>28 (48.3)</td>
<td>36 (55.4)</td>
<td>1.13</td>
<td>0.48 – 2.63</td>
<td>0.78</td>
</tr>
<tr>
<td>institutionalization</td>
<td>24 (41.4)</td>
<td>23 (35.4)</td>
<td>0.96</td>
<td>0.42 – 2.20</td>
<td>0.91</td>
</tr>
<tr>
<td>death</td>
<td>6 (10.3)</td>
<td>6 (9.2)</td>
<td>1.38</td>
<td>0.35 – 5.46</td>
<td>0.65</td>
</tr>
<tr>
<td>Severe clinimetrical decline</td>
<td>12 (27.3)</td>
<td>17 (34.0)</td>
<td>1.46</td>
<td>0.58 - 3.72</td>
<td>0.42</td>
</tr>
<tr>
<td>Combined ‘poor outcome’</td>
<td>34 (58.6)</td>
<td>38 (58.5)</td>
<td>1.23</td>
<td>0.56 – 2.69</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Poor outcome = death, institutionalization, or severe clinical decline (≥1SD deterioration on ≥2 scales). Odds ratios and 95% CI are derived from logistic regression analysis adjusting for age, baseline IDDD, acetylsalicylic acid/coumarin use and acetylcholinesterase-inhibitor use. Difference in deaths in standard care group between fig 1 and table 3: 1 patient died after drop-out, but before 2 years after inclusion-date.
were available. Because patients with AD with varying degrees of cerebrovascular comorbidity according to MRI must have been included also in regular AD trials, it is likely that the disease course in this population would be comparable with those in other AD trials. This was the case\textsuperscript{25,35}, reducing theoretical concerns about the validity of the power analysis.

Significant changes in total cholesterol, low-density lipoprotein cholesterol, homocysteine and folic acid as result of VC, reflect that adherence to prescribed medication was adequate. In contrast, there were no differences with respect to blood pressure levels or body weight after 2 years, suggesting that compliance might not have been optimal in these respects. However, blood pressure decreased significantly during the study in both groups and was close to 140/90 mmHg after 2 years. It remains questionable whether a stricter regime of antihypertensive treatment would have offered patients more benefit, because low blood-pressure has been associated with a greater risk of AD and cognitive decline in late-life.\textsuperscript{37} It is hard to assess exactly the effect in this study of encouraging elderly people to have more physical exercise. It is plausible that well-structured programs may be more efficient than general encouragement from the treating physician as was done in the present study. Some studies suggest that dedicated programs of physical exercise can be beneficial in nursing home residents with dementia and in subjects with memory complaints without dementia, although in the latter group the effect size is small.\textsuperscript{38,39}

All patients in this study had evidence of cerebrovascular lesions on neuroimaging, but few had clinically suffered from a stroke or transient ischemic attack. Therefore, according to current guidelines, there was no indication for acetylsalicylic acid in patients except those with concomitant cardiac or peripheral vascular disease. In the present study, three cases of ICH were encountered in the VC-group. Although this small number of patients precludes a definitive conclusion, the finding is worrisome, because use of aspirin was also associated with fatal ICH in AD patients in a recently published study.\textsuperscript{25} Taken together, these findings suggest that patients with AD who use acetylsalicylic acid might be at greater risk of ICH. A possible reason for this could be that cerebral amyloid angiopathy, which is a pathological finding in as many as 70 to more than 90% of all patients with AD\textsuperscript{40,41}, may render patients prone to ICH, with a possibly more severe course because of the decreased thrombocyte aggregation caused by the acetylsalicylic acid. This suggests that prescription of acetylsalicylic acid might better be avoided in this group of patients, unless there is a clear indication from concomitant cardiovascular disease.

The pragmatic design of the study and its conduct in regular practice may have resulted in several limitations. For example, patients were not under continuous, close surveillance of trial nurses and extensive neuropsychological testing was not performed. However, the external validity of the results of this trial is high. It shows that long term intensive VC for patients with dementia is feasible in daily practice (considering the effects on
laboratory parameters and the relatively limited attrition during a 2-year follow-up), but does not lead to distinct benefits for patients that are detectable using clinically relevant measures of disability, cognitive function and behavioural abnormalities. A possible cause of the disappointing results of VC in the spectrum of patients included in this study could be that the intervention was initiated too late, despite the fact that patients with cognitive deficits that were on average just below conventional cut off values for dementia and with only limited disability were recruited. However, neuropathological changes predate clinical symptoms of dementia and patients who are taken to represent early stages of dementia from a clinical perspective, may already have severe neuropathological abnormalities. Recognition of patients at even earlier stages (e.g. with cognitive impairment without overt dementia and with cerebrovascular lesions as a possible contributor to the deficit) might result in identification of patients who may benefit from meticulous vascular care. Now that it is known that VC is not more expensive than regular care, obtaining even a small clinically relevant benefit will already be cost-effective. In addition, studies in elderly with vascular risk factors but without manifest cognitive impairments, might give answers as to whether earlier treatment might lead to prevention of dementia. At least one study that addresses this issue is in progress. Moreover, in addition to targeting different populations, other types of interventions can be designed that are supported by findings from recent clinical trials concerning vascular risk factors in AD and dementia. These could include more intensive physical exercise, avoiding acetylsalicylic acid and possibly include a higher dosage of a different statin.
References


