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

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Prevention of dementia by intensive vascular care (preDIVA); a cluster-randomized trial in progress
Abstract

**Background and purpose:** Cardiovascular risk factors are associated with an increased risk of dementia. Treatment of hypertension and hypercholesterolemia is associated with a decrease in incident dementia. Whether interventions aimed at cardiovascular risk factors in late life also reduce dementia risk is unknown. Here we report the outline of a pragmatic study that will attempt to answer this question and we describe the prevalence of cardiovascular risk factors in the target population.

**Methods:** We designed a large cluster-randomized trial with a six year follow-up in 3700 elderly subjects (70-78 years) to assess whether nurse-led intensive vascular care in primary care decreases the incidence of dementia and reduces disability. Secondary outcome parameters are mortality, incidence of vascular events and cognitive functioning. Intensive vascular care comprises treatment of hypertension, hypercholesterolemia, diabetes and reducing overweight, smoking cessation and stimulating physical exercise.

**Results:** Baseline data of 1004 subjects show that 87% of the subjects have one or more cardiovascular risk factors and 44% have even two or more risk factors amenable to treatment. 79% of the subjects receiving antihypertensive medication still have a systolic pressure of > 140 mmHg.

**Conclusions:** In this older age group the very high percentage of elderly subjects with cardiovascular risk factors illustrates the large window of opportunity for therapies directed to lower the cardiovascular risk and potentially also the risk for dementia.
Introduction

Increased life expectancy is associated with a steep increase of both the incidence and prevalence of dementia in the elderly. The number of 24.3 million patients that suffer from dementia is projected to almost double every 20 years to 81.1 million by 2040. In addition to personal suffering, this high burden of disease will also have a profound societal impact and, more specifically, it will impose a heavy burden on health care systems at all levels. Strategies aimed at reducing this burden by preventive approaches are currently lacking. Alzheimer’s disease (AD) is by far the most common cause of dementia, followed by vascular dementia (VaD). The previously held sharp distinction between the two may not longer be tenable. Epidemiological studies have documented that vascular risk factors are also risk factors for AD or cognitive decline. Diabetes mellitus, hypertension, hypercholesterolemia, obesity, smoking and lack of physical exercise all contribute to an increased risk of cognitive impairment and dementia. In clinico-pathological studies cerebrovascular lesions and AD pathology are often concomitant and ‘pure AD pathology’ is present in only a minority of dementia cases. Neuroradiological studies have shown that vascular lesions are common in AD patients and the presence of white matter lesions (WML) or ‘silent cerebral infarcts’ in elderly with intact cognition are associated with an increased risk of dementia. These observations have led to the concept of ‘mixed dementia’, referring to patients with both AD pathology and cerebrovascular lesions. The role of vascular risk factors raises the question whether treatment aimed at this component can reduce the risk of incident dementia. All the risk factors mentioned above are modifiable, either by medication or life-style interventions, but randomized clinical trials addressing this important question are rare. Lowering of blood pressure in the elderly, and the use of antihypertensive medication are associated with a decreased risk of dementia, but both a recent Cochrane review and a randomized trial (HYVET) found insufficient evidence for a protective effect of anti-hypertensive treatment in elderly patients. In a small study, improved glycemic control has been associated with better cognitive functions in elderly diabetics, but again a Cochrane review found no convincing evidence relating treatment of diabetes to the prevention of cognitive impairment. Whether treatment of late-life hypercholesterolemia with statins decreases this risk is currently unknown, since research findings are conflicting. There are no data on the effects of life-style interventions aimed at reducing overweight, increasing physical exercise and smoking cessation on dementia risk. Based on the lack of randomized trials to date, some have called for proper cardiovascular primary prevention trials in elderly subjects. Therefore, we designed a randomized clinical trial to assess whether intensive vascular care in the elderly can decrease dementia incidence. Here we describe the outline of the study and present baseline data on the first 1004 participants.
Methods

Objectives
The primary objective of the ‘Prevention of Dementia by Intensive Vascular care’ study (preDIVA) is to assess the efficacy of a multi-component, nurse-led intervention aimed at vascular risk factors in the elderly to prevent dementia or other forms of disability. Secondary objectives are to assess the effects of the intervention on overall mortality, incidence of vascular events including myocardial infarction, stroke, peripheral vascular disease, and on overall changes from baseline in cognitive functioning and mood.

Study design
The multi-site, open, cluster-randomized, parallel group study is carried out in the Netherlands and coordinated from one academic hospital. In order to minimize the Hawthorne effect, general practitioner’s (GP) practices are randomized rather than individual patients. At this time, 65 GP practices have been recruited. A six year long, nurse-led multi-component intervention directed at vascular care is compared to standard care as control condition.

Study population and baseline measurements
All elderly subjects of 70-78 years old within GP practices are invited to participate in the study. The structure of the Dutch healthcare system in which virtually all inhabitants are registered with a GP, minimizes selection bias at this stage. The only exclusion criteria are prevalent dementia and disorders or circumstances expected to interfere with successful long-term follow-up. Education, medical and family history and current medication use are registered and baseline measures for cognitive function and instrumental activities of daily living are recorded in combination with measures relevant for the cardiovascular risk profile. Diet and smoking habits are recorded and the level of physical exercise is assessed using the LASA Physical Activity Questionnaire (LAPAQ). Weight, length, body-mass-index (BMI), abdominal circumference and blood pressure are determined and lipid profile, glucose, homocysteine, CRP, apolipoprotein A-1 and apolipoprotein B are be measured in the blood. Blood is stored for DNA isolation.

Intervention
Whereas randomization takes place at GP level, interventions take place at the individual level, based on the cardiovascular risk profile of each patient. Patients in practices randomized to the standard care (SC) condition receive care as usual according to guidelines for Dutch general practice. All baseline measurements on the risk profile of individual patients are made available for the GP. In the intensive vascular care (IVC) condition, all participants consult a practice nurse every 4 months who addresses smoking habits, level of exercise, diet, body weight
and measures blood pressure with the use of an electronic device. Based on these assessments, both life-style interventions and medical interventions tailored to each individual patient are advised according to a detailed protocol, in accordance with the Dutch GP-guidelines on cardiovascular risk management (table 1). The process quality of delivering IVC at each of the 18 visits in 6 years will be meticulously monitored through regular monitor visits to the practice nurses. Adherence of participants to the

Figure 1. Flow-chart of the study
Table 1. Interventions in patients assigned to intensive vascular care

<table>
<thead>
<tr>
<th>Component</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>assessment current levels of physical activity</td>
</tr>
<tr>
<td></td>
<td>individualized advice regarding physical activity</td>
</tr>
<tr>
<td>Smoking</td>
<td>assessment smoking status</td>
</tr>
<tr>
<td></td>
<td>assessment readiness to quit</td>
</tr>
<tr>
<td></td>
<td>if indicated: nicotine-replacement therapy, behavioral advice or counseling</td>
</tr>
<tr>
<td>Weight</td>
<td>BMI &gt; 25 : behavioral and nutritional counseling is offered</td>
</tr>
<tr>
<td></td>
<td>20 &gt; BMI &gt; 30: referral to dietician</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>SBP 130-139 mmHg or DBP 85-89 mmHg: lifestyle modifications (exercise,</td>
</tr>
<tr>
<td></td>
<td>weight, sodium restriction, moderation of alcohol intake, cessation of</td>
</tr>
<tr>
<td></td>
<td>smoking, stopping of NSAID’s)</td>
</tr>
<tr>
<td></td>
<td>SBP ≥ 140 mmHg or DBP ≥ 90: stepped care drug-therapy</td>
</tr>
<tr>
<td>Blood lipids</td>
<td>subjects with known CVD: statin (e.g. simvastatin 40 mg)</td>
</tr>
<tr>
<td></td>
<td>subjects without known CVD but with TC/HDL ratio &gt; 5: statin</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>measured yearly and treated according a stepped care protocol if exceeding</td>
</tr>
<tr>
<td></td>
<td>6.1 mmol/l (110 mg/dl)</td>
</tr>
<tr>
<td>Cardiovascular history</td>
<td>subjects having clinical manifestations of vascular disease will receive</td>
</tr>
<tr>
<td></td>
<td>Acetylsalicylic acid (100 mg) (or anti-thrombotic therapy, if indicated)</td>
</tr>
</tbody>
</table>

BMI = body mass index (kg / m²), SBP = resting systolic blood pressure, DBP = resting diastolic blood pressure, CVD = cardiovascular disease, TC = total cholesterol, HDL = high density lipoprotein; NB: In subjects with a SBP > 140, but without CVD and with a low risk profile, an attempt can be made to lower the BP with lifestyle modifications only.

intensive vascular care regimen will be recorded and reasons for non-compliance will be explored. Drop outs will be actively retrieved in order to minimize attrition.

**Follow up and primary outcome parameters**

All baseline measurements will be repeated after 2, 4 and 6 years in all patients. The primary outcome parameters are incident dementia and the change from baseline in disability as measured by the AMC Linear Disability Scale (ALDS). The GP will be advised to refer patients with cognitive decline to a geriatric or neurological outpatient clinic. Reasons for referral are (1) memory complaints of patients or caregivers or (2) decline of MMSE score at one of the two yearly assessments (2 points or more from preceding visit, or 3 points or more from baseline visit, irrespective of absolute scores). The physician analyzing the suspected cognitive decline is requested to fill out a questionnaire based on international diagnostic criteria for the most common forms of dementia, including the results of ancillary investigations like neuropsychological assessment, laboratory tests and imaging. This information is then presented to an independent auditing committee, blinded for the treatment allocation. This committee will classify the type of dementia (possible/probable Alzheimer’s disease, vascular dementia, frontotemporal dementia, Lewy body dementia, and dementia not otherwise specified). The patient will continue in the study as planned and will be re-assessed after one year, when the blinded auditing committee will establish a definitive diagnosis.
Secondary outcome parameters

Secondary outcome parameters are mortality, incidence of vascular events including myocardial infarction, stroke, and peripheral vascular disease. Mood is assessed with the Geriatric Depression Scale (GDS). Cognitive functioning will be assessed using the Mini Mental Status Examination (MMSE) for overall cognition and the Visual Association Test (VAT), which is a memory task sensitive to early stages of AD. All participants will be assessed for study outcomes after two, four and six years.

Sample size calculation and randomization

For eligible patients, the age-specific incidence of dementia increases from 0.2% at 70 to 2.0% at 78 years. Thus, the cumulative incidence of dementia after 6 years mounts up to 4.0% to 16.2% respectively, for participants that are 70 to 78 years old at baseline. After correcting for the relative under-representation of older participants (based on Dutch life tables), the mean cumulative risk for dementia over the study period is estimated to be 8.24%. With a power of 80% and a two-sided significance level of 5%, enrolment and follow-up of at least 2774 participants would be needed to detect a reduction of dementia incidence by a third to 5.49% in the IVC group. However, analysis of individual patients from a cluster randomized trial will lead to a loss of power. At an estimated intracluster correlation of 0.01 and an average cluster size of 25, this design effect would mount up to 1.24, yielding an effective sample size of 2237. This would reduce the power of the study to 73%. To compensate for this design effect and for attrition, both of unknown magnitude, the final target sample of participants was increased to 3700.

GP’s are usually organized in health-centers and the number of practices per health-centre varies between 3 and 7. In order to achieve an overall 1:1 ratio of participants in both conditions and to ensure that at least one GP practice in each health-centre is allocated to the experimental condition, a centralized computer based randomization program is used. After completion of all baseline measurements in one health-centre, the GP practices are randomized as one block by this computer program. Subsequently the participants and GP’s are informed to which condition their practice has been allocated.

Statistical analysis

Statistical analysis will be based on estimates of cumulative dementia incidence according to the Kaplan–Meier method, the difference between groups will be evaluated by means of the log-rank test, adjusted for clustering in the data and for competing risk of death, since treatment of case fatalities as censored observations tend to inflate estimates of cumulative incidence. All various forms of morbidity other than dementia that can be expected to occur will ultimately translate into increasing disability that will affect scores on the other primary outcome, the ALDS. The generic nature of this scale makes the ALDS especially suitable as one of the primary outcome measures. Baseline characteristics such as age, sex, education, baseline cognitive function, disability and cardiovascular risk profile will be included in the models. Additional analyses will be
performed with corrections for the actual degree of vascular care that was provided. After 4 years of follow-up, a masked interim-analysis will be performed based on ALDS scores. An independent committee will advise on the continuation of the study.

**Safety and ethical and legal aspects**

All presumed adverse events (AEs) are assessed and the intensity of AEs will be graded as mild, moderate, or severe. AEs will be reported to the Clinical Research Office as either possibly related or unrelated to study procedures. The study protocol has been approved by the medical ethical committee of the Academic Medical Centre. A four member Steering Committee has been formed that has the authority to terminate participation of a general practice (e.g. failure to comply with the protocol) or the trial as a whole (e.g. safety concerns or on advice of the interim analysis committee). Subjects participate on a voluntary basis after providing informed consent and can decide to leave the study any time without the need to legitimize their decision.
Results

Between June 2006 and December 2007, 2500 participants have been recruited and inclusion is ongoing. The last 6-year follow up assessments are expected not before March 2014. The first 1004 participants belonged to 31 different GP practices, generating an average cluster size of 26. Baseline characteristics are summarized in table 2, providing a first estimate of the characteristics of the entire population under study. Of the 523 subjects (52.1%) using antihypertensive drugs, 77.6% still have a systolic BP > 140 mmHg. Overall, only 53.8% of the subjects with a systolic BP > 140 mmHg use antihypertensive drugs. For a diastolic BP > 90 mmHg these numbers are 16.6% and 54.4% respectively. In 11.1% of the subjects total cholesterol is ≥ 6.5 mmol/l (117 mg/dl), and only 15.3% of these use a statin, leaving 84.7% undertreated. Of the participants who do use a statin, only 5.1% still have a total cholesterol ≥ 6.5 mmol/l. Overweight defined as a BMI ≥30 is present in 28.4% of the participants. Lack of physical exercise is present in 9.4% of the subjects according to the WHO guideline which recommends at least 30 minutes of moderate exercise at least 5 times a week.

Examination of five risk factors that are amenable to intervention (systolic or diastolic hypertension, overweight, elevated serum cholesterol, smoking and lack of physical exercise) provides estimates of the fraction of subjects in which the risk of dementia or cardiovascular complications can potentially be reduced (fig 2a). Most subjects have one (46.1%) or two (32.8%) modifiable risk factors. In this cohort a total of 87% of the participants have at least one modifiable risk factor (fig 2b), leaving only 13% of participants without an indication for counseling or treatment at baseline.

When stratified into subjects with and without previous cardiovascular disease or stroke, there was no difference in number of currently present risk factors (p = 0.84,
linear by linear association $p = 0.58$). Comparing subjects with a previous cardiovascular disease or stroke ($N = 363$, 36.2%) with participants without these complications ($N = 641$, 63.8%), the former do have a lower systolic BP (154.6 vs. 157.8, $p = 0.02$), lower diastolic BP (78.6 vs. 81.1; $p < 0.001$) and lower cholesterol (5.5 vs. 4.7; $p < 0.001$), suggesting a treatment effect of the secondary preventive strategies that have already been initiated based on the medical history.

**Discussion**

The high percentage of elderly with one or more cardiovascular risk factors that are not sufficiently treated clearly illustrates the window of opportunity for improved cardiovascular risk management. This is remarkable considering the overwhelming amount of evidence from epidemiological studies on risk factors for cardiovascular disease and all current knowledge about the importance of these risk factors. A recently published dementia risk score for middle-aged people, based on age, education, sex, systolic and diastolic BP, BMI, total cholesterol and physical activity, contains several factors that are amenable to intervention. Following this line of reasoning, the risk of developing dementia can potentially be reduced in 87% of our study population (fig 2b).

Even though our study was primarily designed to prevent dementia and other forms of disability, it is likely that an effect will be sorted on several cardiovascular events like myocardial infarction and peripheral vascular disease as well. If this study will show a benefit from IVC, it is anticipated that this will lead to a greater awareness that also in the elderly strict management of cardiovascular risk profile is warranted. Until now most data on vascular risk factors and dementia come from large population-based cohorts, and represent repeated documentation of associations. The little data available on intervention effects come from large cardiovascular studies using dementia as a secondary outcome parameter, and are mostly performed in younger patients. Recently data have been published from a large study assessing the effect of blood pressure lowering in the very elderly (over 80 years of age). The reduction of cardiovascular disease including stroke was such that early termination was warranted due to ethical considerations. No statistically significant effect on cognition was found, but the mean follow-up was only 2.2 years, and a reduction in incident dementia in the treatment group was certainly suggested by the data. These data are encouraging to continue investigating the effect of better vascular care in the elderly on incident dementia.

We deliberately chose to perform the IVC intervention in GP practices, because this allowed access to a relatively unselected population in comparison to participants that are recruited through academic centers or by advertisements. Moreover, we think that the nurse-led intervention in GP practices offers an interesting model for organizing IVC. A limitation of this design could be that it is performed in only one country, with
a health care system with specific characteristics that may be difficult to translate to
countries without a well-organized GP-structure.
A potential concern from a theoretical point of view may be the degree of contrast
between the control group receiving SC and the experimental IVC group. Identification
of cardiovascular risk factors at baseline in both treatment conditions may also
stimulate interventions in the control group. However, several observations suggest
that important differences between the two conditions will be retained throughout
the study. Firstly, extensive documentation of difficulties with the implementation of
interventions aimed at cardiovascular interventions (even in specialized centers for
secondary prevention) makes it highly unlikely that participants in the SC condition
will receive vascular care to such a degree that the contrast with the IVC condition
will be jeopardized. Surveys show that only 30% of hypertensive patients are treated
adequately and less than 50% of cardiac patients receive proper care, estimates
consistent with our first baseline measurements. 13, 18 Secondly, if preventive measures
are started, such as statin therapy in reducing cardiovascular morbidity, adherence
to drug therapy in the elderly declines sharply after a short period, to only 43% after
6 months for statin therapy. 20 Thirdly, it is documented that nurse-led secondary
prevention in primary care improved medical and lifestyle components of prevention
compared to standard care in a randomized controlled trial, with large differences
in the proportions of patients with appropriate prevention. 16 Finally, randomized
controlled trials of secondary prevention programmes repeatedly documented that
disease management programmes improve the processes of care in patients with
coronary heart disease in comparison to standard care. 15
It could be argued that preventive measures should start well below the age of 70 years.
However, at younger ages the incidence of dementia is below 0.2%, thus requiring
studies with either tens of thousands of participants or a follow-up period of more than
a decade in order to be able to document a reduction of dementia incidence. Since
age is the most important risk factor for dementia, we sought a practicable balance
by aiming at 6 years follow-up of 3700 elderly between the ages of 70 and 78 years. An
upper age limit was included to minimize attrition during six year follow-up, which can
be expected to be very high in the age group above 78 years.
If the approach of multi-component intensive vascular care turns out to be effective in
terms of reducing either the incidence of dementia or progression of disability over time,
it will be difficult to conclude exactly which aspect of the intervention has contributed
most to the effect. On the other hand, a positive study result will certainly stimulate
drastic changes in the approach of elderly subjects and will provide a sound basis for
widespread implementation of vascular care in order to increase the level of ‘healthy
aging’. A perspective on risk reduction for dementia will surely have a great impact on
patients’ and doctors’ perception of preventive measures, thus stimulating all parties
involved to put more effort in preventive measures in order to avert the heavy burden
of dementia and vascular disease in the elderly.
Reference List


