Vascular factors in dementia: prevention and pathology
Richard, E.
Methodological issues in a cluster-randomized trial to prevent dementia by intensive vascular care

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Abstract

Objectives: Description of methodological issues in a trial designed to evaluate if a multi-component intervention aimed at vascular risk factors can prevent dementia.

Design, setting and participants: Multi-center, open, cluster-randomized controlled clinical trial (preDIVA) including 3535 non-demented subjects aged 70-78, executed in primary practice and coordinated from one academic hospital. General practices are randomized to standard care or intensive vascular care.

Intervention: Vascular care consists of 4-monthly visits to a practice nurse who monitors all cardiovascular risk factors. Hypertension, hypercholesterolemia, overweight, lack of physical exercise and diabetes are strictly controlled according to a protocol and treated in a way, tailored to the characteristics of individual participants.

Measurements: Primary outcomes are incident dementia and disability; secondary outcomes are mortality, vascular events (stroke, myocardial infarction, peripheral vascular disease), cognitive decline and depression.

Results: Between May 2006 and February 2009, 3535 subjects from 115 general practices have been included. The clusters have an average size of 31 (SD 22, range 2-114). 1658 Patients from 52 practices were randomized to the standard care condition and 1877 patients in 63 practices to the vascular care condition.

Discussion: When designing a cluster-randomized trial, clustering of patient data within GP practices leads to a loss of power. This should be adjusted for in the power calculation. Since intensive vascular care will probably lead to a reduction in cardiovascular mortality, the competing risks of mortality and dementia should be taken into account.
Introduction

Cardiovascular risk factors including hypertension, diabetes mellitus, hypercholesterolemia, overweight and lack of physical exercise are all independent risk factors for dementia.\textsuperscript{1} The most common form of late-onset dementia is Alzheimer’s disease (AD), followed by vascular dementia (VD). Cerebrovascular lesions (white matter lesions and cerebral infarcts) are commonly found on magnetic resonance imaging (MRI) and post-mortem examination in AD and probably contribute to dementia severity.\textsuperscript{2,3} In spite of the consistent associations between vascular risk factors and incident dementia, to date it is unclear whether treatment of these risk factors can actually prevent or delay the onset of dementia in the elderly. The objective of the preDIVA study (prevention of dementia by intensive vascular care) is to evaluate whether multi-component vascular care executed in primary practice can prevent dementia. Here we highlight some important methodological issues that are intrinsic to cluster randomized trials for the prevention of dementia in primary care.

Methods

Subjects, Intervention, follow-up and outcome parameters

All subjects aged 70-78 in 115 primary care practices were invited to participate. Exclusion criteria were dementia and medical conditions or circumstances expected to interfere with long-term follow-up. Subjects were randomized to either standard care (SC) according to general practitioner guidelines or intensive vascular care (VC), coordinated by a practice nurse under supervision of the general practitioner (GP) (table 1). Subjects in the VC group are followed 4-monthly, during which visits all prevalent vascular risk factors and compliance with initiated therapy are assessed. The

<table>
<thead>
<tr>
<th>Component</th>
<th>intervention</th>
</tr>
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<tbody>
<tr>
<td>Blood pressure</td>
<td>&gt;130/85: lifestyle modifications</td>
</tr>
<tr>
<td></td>
<td>&gt;140/90: stepped care drug therapy</td>
</tr>
<tr>
<td>Lipid level</td>
<td>With CVD: statin (e.g. simvastatin 40 mg)</td>
</tr>
<tr>
<td></td>
<td>Without CVD: if TC/HDL ratio &gt; 5: statin</td>
</tr>
<tr>
<td>Weight / Exercise</td>
<td>BMI&gt;25: counselling about nutrition / exercise</td>
</tr>
<tr>
<td></td>
<td>BMI &lt;20 / &gt;30: referral dietitian and counselling about exercise</td>
</tr>
<tr>
<td>Blood glucose (yearly)</td>
<td>&gt;6.1 mmol/l: treat according to stepped protocol</td>
</tr>
<tr>
<td>Smoking</td>
<td>If yes: counselling, nicotine replacement to assist quitting</td>
</tr>
<tr>
<td>Cardiovascular history</td>
<td>If yes: aspirin 100 mg (or coumarin if indicated)</td>
</tr>
</tbody>
</table>

CVD: cardiovascular disease, TC: total cholesterol, HDL: high density lipoprotein, BMI: body mass index
interventions in table 1 are according to a protocol, but tailor-made to each individual patient, depending on the presence of risk factors. The primary outcome parameters are incident dementia, assessed with current guidelines (AD, VD, dementia with Lewy bodies, frontotemporal dementia and dementia not otherwise specified) and disability as measured with the AMC Linear Disability Scale (ALDS). Secondary outcome parameters are mortality, vascular events (stroke, myocardial infarction, peripheral vascular disease), cognitive decline and depression.

**Design, sample size calculation and power**

The preDIVA study is a multicenter, open, cluster-randomized controlled clinical trial in primary practice, coordinated from one academic hospital with a 6-year follow-up. Instead of randomizing individual patients, general practices ('clusters') are randomized, while individual patient data will be analyzed. (Fig 1) We based our sample size calculation on the age-specific risk of dementia over six years, corrected for a skewed distribution towards the left based on Dutch life-tables. (Fig 2) To detect a reduction of incident dementia of 33% (from 8.24% to 5.49%) with 80% power and $\alpha$ set at 0.05, 2774 subjects would be needed.

But when analyzing individual patient data from a cluster-randomized trial, power is always reduced due to similarities (e.g. socioeconomic, ethnic) between subjects within the clusters and the intra-cluster correlation coefficient rho ($\rho$) should be calculated.\(^5\)

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**Figure 1.** Trial design
Using the cluster-size and the intra-cluster correlation coefficient for the parameter under study, the ‘design-effect’ can be calculated, and this should be corrected for in the sample size calculation. The expected average cluster-size was 25 and we estimated the average $\rho$ to be 0.01. The design-effect can be calculated using the formula $\rho \cdot (m - 1) + 1$, in which $m = \text{cluster size}$. Using this formula, the design-effect would be $0.01 \cdot (25 - 1) + 1 = 1.24$, leading to an effective sample size of $2774/1.24 = 2237$ subjects. Correcting for this design-effect and an unknown attrition, the sample size was targeted at 3700.

Baseline measurements were obtained before randomization of the respective practices. This order of events was chosen to prevent a hypothesized selective drop-out of subjects randomized to the standard care, after revealing that they would receive usual care.

**Results**

Between May 2006 and March 2009 3535 non-demented elderly subjects from 115 general practices were recruited for inclusion in this study (1658 SC vs. 1877 VC). A temporary stagnation in inclusion occurred due to the need to recruit new GP practices.
and subsequently implement the study protocol in order to reach the target sample size. The average cluster size is 31 (SD 22, range 2-114). Only 12 % of the subjects have no potentially modifiable vascular risk factors, defined as blood pressure >140/90 mm Hg, total cholesterol >6.5, body mass index >30 Kg/m², glucose>6.1 mmol/l and current smoking. Lack of physical exercise is not included in this definition. Most subjects have at least one (46%) or two (32%) risk factors. (Fig 3)

**Discussion**

The baseline data of this trial show that it is feasible to recruit over 3500 elderly non-demented subjects, although with 34 months it took longer than planned, due to time-consuming recruitment of new practices. Most of the subjects have one or more cardiovascular risk factors potentially amenable to treatment, offering a large opportunity for improving cardiovascular risk management. Several methodological issues of this study have to be addressed. We deliberately chose to perform this large intervention trial in primary practice, because this leads to high external validity of the results. If the intervention proves effective, its implementation is within easy reach of most GP practices, without creating a heavy burden to the already busy schedule of GPs or to the health care system as a whole. With this type of intervention (open, individualized) in primary care the cluster-randomized design is essential, but the problem of intra-cluster correlations may affect the power and should always be taken into account when designing this type of trial.

A concern from a theoretical point of view is the contrast between the groups. The baseline measurements are revealed to the GPs, which could possibly lead to a better treatment in case of present risk factors in the SC group, jeopardizing the contrast between the groups. However, our baseline data show that many patients have undertreated cardiovascular risk factors, in spite of the efforts made by GPs to treat according to extensive GP guidelines as available in The Netherlands. It is unlikely that one baseline measurement will result in significantly better long-term control of
vascular risk factors without the frequent and extensive consultations of the practice nurse.
One could argue that preventive measures should start earlier than 70 years of age, in order to have a preventive effect. However, the very low incidence of dementia in this age group would imply that a very long follow-up and much larger sample size would be required, which is most probably not feasible in an intervention trial.
In addition to its possible effects on a reduction in incident dementia, it is likely that our intensive vascular care will also lead to a reduction in cardiovascular morbidity and mortality. Mortality can be considered as a competing risk for dementia, especially because age is the strongest risk factor for dementia. It is therefore conceivable that a reduction in mortality in the VC group leads to an actual increase of absolute number of cases of incident dementia. In the final analysis we will have to correct for this competing risk.7
Reference List


