Prevention of Dementia by Intensive Vascular care: lessons learned from an ongoing pragmatic, cluster randomized trial

NIH Collaboratory Grand Rounds Jan 23rd 2015

Pim van Gool & Edo Richard
Department of Neurology, Academic Medical Center, Amsterdam, The Netherlands

No conflict of interest
clinical domain | gradually progressive dementia

Auguste D.
Frankfurt, 1902
clinical domain
neuropathology

gradually progressive dementia
Alzheimer encephalopathy
adapted from Savva et al. NEJM 2009
clinical domain
neuropathology

severe, isolated
Alzheimer encephalopathy
The two faces of Alzheimer's disease
Van Gool, Eikelenboom
J Neurol, 2000; 247: 500-505
The two faces of Alzheimer's disease
Van Gool, Eikelenboom
J Neurol, 2000; 247: 500-505

clinical domain
neuropathology

clinical domain
neuropathology

severe, isolated
Alzheimer encephalopathy

Type I

Type II

mild/moderate
Alzheimer encephalopathy

vascular
lesion
burden
The two faces of Alzheimer's disease
Van Gool, Eikelenboom
J Neurol, 2000; 247: 500-505

Viswanathan et al. Neurology 2009

clinical domain
neuropathology

type I
severe, isolated Alzheimer encephalopathy

Type II
mild/moderate Alzheimer encephalopathy

Neurodegenerative burden
Vascular cerebral lesion burden

Viswanathan et al. Neurology 2009
SOURCE: UK Alzheimer Society
window of opportunity for prevention

The projected effect of risk factor reduction on Alzheimer’s disease prevalence

Deborah E Barnes, Kristine Yaffe

Lancet Neurology 2011

50% of dementia attributable to vascular risk factors
The projected effect of risk factor reduction on Alzheimer’s disease prevalence

Deborah E Barnes, Kristine Yaffe

50% of dementia attributable to vascular risk factors

Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study

Miia Kivipelto, Tiia Ngandu, Tiina Laatikainen, Bengt Winblad, Hilkka Soininen, Jaakko Tuomilehto

non-modifiable

• age
• education
• sex

modifiable

• blood pressure
• diabetes
• physical exercise
• cholesterol
blood pressure

HYVET-Cog


placebo
active 1.5 mg indapamide

HR 0.86 (CI 0.67-1.09) p=0.21
blood pressure

HYVET-Cog


HR 0.86 (CI 0.67-1.09) p=0.21
Prevention of Dementia by Intensive Vascular care

“I am only 77 years old, so I will be around for another 23 years at least!”
<table>
<thead>
<tr>
<th>age</th>
<th>Age-specific cumulative risk over 6 years</th>
<th>Average cumulative risk over 6 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>4.4%</td>
<td></td>
</tr>
<tr>
<td>....</td>
<td></td>
<td>8.24%</td>
</tr>
<tr>
<td>78</td>
<td>16.2%</td>
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</table>
## Sample Size

<table>
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<td>78</td>
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<td></td>
</tr>
</tbody>
</table>

33% risk reduction (8.2 → 5.5) : 2774 participants

Compensate for unknown drop-out and $\rho$ (rho) → 3700

Richard et al. J Nutr Health Aging 2010
preDIVA - time line
preDIVA - time line
preDIVA - time line

First subject out

Last subject out
Prevention of Dementia by Vascular care

121 general practices
25 practice nurses

3533 participants

baseline measurement

cluster randomization

standard care
53 practices
1656 subjects

vascular care
68 practices
1877 subjects

70-78 years
no dementia
6 yrs follow-up likely
Prevention of Dementia by Vascular care

- **3533 participants**
  - baseline measurement
  - cluster randomization
    - **standard** care
      - 53 practices
      - **1656** subjects
    - **vascular** care
      - 68 practices
      - **1877** subjects
standard care (1656)

vascular care (1877)

4-monthly visits (nurse): 18 visits

2 year dementia? handicap

4 year dementia? handicap

6 year dementia? handicap
Secondary outcomes:
- stroke
- myocardial infarction
- cognitive decline
- depression
- mortality

- standard care (1656)
- vascular care (1877)

4-monthly visits (nurse): 18 visits

2 year dementia? handicap
4 year dementia? handicap
6 year dementia? handicap
**standard** care (1656)

**vascular** care (1877)

4-monthly visits (nurse): 18 visits

Secondary outcomes:
- stroke
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- mortality

<table>
<thead>
<tr>
<th>Component</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>lifestyle, medication</td>
</tr>
<tr>
<td>Smoking</td>
<td>quit, counseling</td>
</tr>
<tr>
<td>Exercise</td>
<td>advice, exercise program</td>
</tr>
<tr>
<td>Overweight</td>
<td>BMI&gt;25: advice; BMI&gt;30: dietician</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>CVD: statin; no CVD: in case TC/HDL &gt;5: statin</td>
</tr>
<tr>
<td>Glucose</td>
<td>if &gt; 6.1 mmol/l: stepped protocol</td>
</tr>
</tbody>
</table>
## Vascular Care

### Practice Nurses

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<td>Advice, exercise program</td>
</tr>
<tr>
<td>Overweight</td>
<td>BMI &gt; 25: advice to exercise and dietary change; BMI &gt; 30: dietician</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>CVD: statin; no CVD: in case TC/HDL &gt; 5: statin</td>
</tr>
<tr>
<td>Glucose (fasting)</td>
<td>If ↑: stepped treatment protocol</td>
</tr>
<tr>
<td>Cardiovascular history</td>
<td>Acetylsalicylic acid 100 mg</td>
</tr>
</tbody>
</table>
baseline

Systolic BP

BMI

Total cholesterol

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>&lt;120</td>
<td>5%</td>
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<tr>
<td>120-140</td>
<td>20%</td>
</tr>
<tr>
<td>140-160</td>
<td>40%</td>
</tr>
<tr>
<td>160-180</td>
<td>25%</td>
</tr>
<tr>
<td>&gt;180</td>
<td>10%</td>
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<table>
<thead>
<tr>
<th>Category</th>
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<tr>
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<tr>
<td>4.1-5</td>
<td>10%</td>
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<tr>
<td>5.1-6</td>
<td>25%</td>
</tr>
<tr>
<td>6.1-7</td>
<td>15%</td>
</tr>
<tr>
<td>&gt;7</td>
<td>5%</td>
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baseline

Systolic BP

<table>
<thead>
<tr>
<th>Range</th>
<th>%</th>
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<tr>
<td>&lt;120</td>
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<td>120-140</td>
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<tr>
<td>140-160</td>
<td>35%</td>
</tr>
<tr>
<td>160-180</td>
<td>39%</td>
</tr>
<tr>
<td>&gt;180</td>
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BMI

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<tbody>
<tr>
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<td>4%</td>
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</tr>
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Total cholesterol

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</table>
• lack of physical exercise 40%
• smoking 12%
preDIVA – preliminary results

• effects at 2 year follow up on blood pressure
• association of apathy with cardiovascular risk
• findings in qualitative study
• preliminary figures follow-up
preDIVA – preliminary results

N = 2200, T= 2 years

systolic blood pressure

<table>
<thead>
<tr>
<th></th>
<th>intervention</th>
<th>control</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>160</td>
<td>140</td>
</tr>
<tr>
<td>2 year</td>
<td>150</td>
<td>145</td>
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</table>

mmHg

- 7.9

- 3.4

mmHg

diastolic blood pressure

<table>
<thead>
<tr>
<th></th>
<th>intervention</th>
<th>control</th>
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<tr>
<td>baseline</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>2 year</td>
<td>85</td>
<td>80</td>
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</table>

- 2.4

- 0.8

baseline

2 year
Geriatric Depression Scale: Short Form

Choose the best answer for how you have felt over the past week:

1. Are you basically satisfied with your life? **YES / NO**
2. Have you dropped many of your activities and interests? **YES / NO**
3. Do you feel that your life is empty? **YES / NO**
4. Do you often get bored? **YES / NO**
5. Are you in good spirits most of the time? **YES / NO**
6. Are you afraid that something bad is going to happen to you? **YES / NO**
7. Do you feel happy most of the time? **YES / NO**
8. Do you often feel helpless? **YES / NO**
9. Do you prefer to stay at home, rather than going out and doing new things? **YES / NO**
10. Do you feel you have more problems with memory than most? **YES / NO**
11. Do you think it is wonderful to be alive now? **YES / NO**
12. Do you feel pretty worthless the way you are now? **YES / NO**
13. Do you feel full of energy? **YES / NO**
14. Do you feel that your situation is hopeless? **YES / NO**
15. Do you think that most people are better off than you are? **YES / NO**
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15. Do you think that most people are better off than you are? **YES / NO**
Cross-sectional associations

In participants *without* depressive symptoms (N=2848)

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<tr>
<td>Stroke</td>
<td><strong>1.8</strong> (1.4-2.3)</td>
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<td>Cardiovasc disease</td>
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*Adjusted for age, gender, education, MMSE, ADL-functioning, polypharmacy

*OR for every point increase in apathy score
Cross-sectional associations

In participants without depressive symptoms (N=2848)

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*Adjusted for age, gender, education, MMSE, ADL-functioning, polypharmacy

*OR for every point increase in apathy score

---

Systolic BP: $P = 0.03$

BMI: $P = 0.002$

Type II DM: $P = 0.07$
Apathy is an independent risk factor for incident cardiovascular disease in the older individual: a population-based cohort study

Lisa S. M. Eurelings¹, Suzanne A. Ligthart², Jan Willem van Dalen¹, Eric P. Moll van Charante², Willem A. van Gool¹ and Edo Richard¹

<table>
<thead>
<tr>
<th>Baseline apathy score on GDS-3A</th>
<th>RRi incident CVD and strokeᵃ</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>CVD</td>
<td>968</td>
</tr>
<tr>
<td>1</td>
<td>stroke</td>
<td>419</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>128</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>29</td>
</tr>
</tbody>
</table>

cardiovascular disease HR 3.52 (1.82-6.81)

stroke HR 0.91 (0.32-2.59)
meta-analysis of individual patient data (N ≈ 28,000)
(England, Australia, China, Germany, Italy, Netherlands, Singapore, United States of America)
Perspectives of older people engaging in nurse-led cardiovascular prevention programmes:
a qualitative study in primary care in the Netherlands

• Motivators to participation
• Barriers to continuation
• Facilitators of continuation
Motivators to participation: reassurance

‘We [my wife and I] expected that we would find out how we were doing, intellectually [as well as physically]. I was rather interested in that. I wanted to know how I was doing.’ (P9, male, 77 years, living with partner, ongoing participation)

‘Your blood pressure is measured and once in a while she checks the blood. [...] Normally, when you don’t have any complaints, you don’t visit the doctor, right? It feels unnecessary. So I’m glad we have this now, it makes me feel very safe.’ (P5, female, 78 years, living with partner, ongoing participation)
Barriers to continuation: lack of trust

‘Those youngsters, they might be nice people but not someone to begin a conversation with. Especially not when you’re past 75 [years of age]. No experience of life. [...] The difference with [the former nurse] was huge; she was in really close contact with you.’ (P12, female, 81 years, living alone, discontinued participation)

‘I know what a healthy diet is. Not that I always do what’s best for my health, but I do know what it is. [...] There was no advice at all that was useful to me. They were all things that I already knew. Lifestyle advice, I think that’s meddlesome. But that’s unkind to say.’ (P7, male 77 years, living alone, discontinued participation)
Facilitators to continuation: coaching attitude / autonomy

‘No, no, I don’t think so. We did talk about certain things, but it was not advice but um... more like a conversation. What you can do to maintain your weight, those kind of things.’ (P3, female, 77 years, living with partner, ongoing participation)

‘She never tells us [my daughter and me] what to do, not at all. She likes it when I tell her, that’s why she’s so good. We live healthier now. We eat two pieces of fruit every day, she always asks about it. Yes; we eat very healthy as a matter of fact.’ (P1, female, 77 years, living with daughter, ongoing participation)

‘Actually, I have this point of view. I absolutely hate sports and such matters. So I will not do it. I’ll probably live for a few less years: so what.’ (P2, female, 77 years, living alone, ongoing participation)
preliminary figures* follow-up

* preliminary figures, subject to change during continuous follow-up
**preliminary figures** follow-up

3533 baseline assessments

- 2937 2 yr assessments
- 2308 4 yr assessments
- ±1870 6 or 6+ yr assessments

459 deceased or demented

more than ±3153 (>89.3%) in final analysis of primary outcome

* preliminary figures, subject to change during continuous follow-up
1. A simple clinically relevant primary outcome is a prerequisite for a high rate of follow-up after 6+ years in a population of older persons.
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2. A long-term pragmatic trial may also inspire serendipitous findings (apathy)
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2. A long-term pragmatic trial may also inspire serendipitous findings (apathy).

3. Add-on, qualitative studies provide new insights that are important for future studies.
1. A simple clinically relevant primary outcome is a prerequisite for a high rate of follow-up after 6+ years in a population of older persons

2. A long-term pragmatic trial may also inspire serendipitous findings (apathy)

3. Add-on, qualitative studies provide new insights that are important for future studies

4. preDIVA has been a launching platform for European collaboration
ongoing dementia prevention RCTs

<table>
<thead>
<tr>
<th>Sample size</th>
<th>preDIVA (Netherlands)</th>
<th>FINGER (Finland)</th>
<th>MAPT (France)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3534</td>
<td>1200</td>
<td>1680</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>preDIVA</th>
<th>FINGER</th>
<th>MAPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>not demented 70-78 y</td>
<td>dementia risk score &gt; 6 60-75 y</td>
<td>memory complaint or frailty &gt; 70 y</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multi-domain intervention</th>
<th>preDIVA</th>
<th>FINGER</th>
<th>MAPT</th>
</tr>
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<tbody>
<tr>
<td>nurse-led vascular care, diet advice, exercise advice</td>
<td>vascular care, diet advice, exercise, cognitive training</td>
<td>vascular care, diet advice, exercise advice, cognitive training</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th>preDIVA</th>
<th>FINGER</th>
<th>MAPT</th>
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<tbody>
<tr>
<td>6 y</td>
<td>2 y</td>
<td>3 y</td>
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<th>Primary outcome</th>
<th>preDIVA</th>
<th>FINGER</th>
<th>MAPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>dementia, disability</td>
<td>change in cognitive function</td>
<td>change in cognitive function</td>
<td></td>
</tr>
</tbody>
</table>

N total = 6414
European Dementia Prevention Initiative

www.edpi.org
timing of intervention

middle age  60  70  old age

effect too low

effect of intervention

Timing of intervention

Incidence too low
Effect too low

Effect of intervention
Dementia incidence

Middle age 60 70 Old age

timing of intervention

The timing of intervention is critical in managing dementia incidence. The optimal window for intervention is before the most realistic window for outcome assessment, as the incidence of dementia is too low and the effect of intervention is too low during this period. The optimal window for intervention is when the incidence is high and the effect of intervention is maximized. The late stages (70+ years) are too late for intervention to be effective, and the middle ages are also not optimal due to low incidence and effect. Therefore, the most realistic window for intervention is between 60 and 70 years old, where the incidence is high and the effect is significant. 

Healthy Aging Through Internet Counseling in the Elderly

Aim

Improve vascular risk factor management to prevent cognitive decline, dementia and cardiovascular disease
rationale

• current cardiovascular prevention strategies moderately effective
• adherence limited → self-management, ownership
• most interventions target one risk factor – most elderly have multiple
• Syst review: 4 RCTs on efficacy internet interventions in elderly
rationale

• current cardiovascular prevention strategies moderately effective
• adherence limited → self-management, ownership
• most interventions target one risk factor – most elderly have multiple
• Syst review: 4 RCTs on efficacy internet interventions in elderly

Why internet-based?

- Generic
- Widely implementable
towards an interactive intervention platform

**Focusgroups:**
- Target population
- Nurses
- Doctors
Gerelateerde doelen

- Vanaf morgen zal ik proberen om mijn fiets meer te...
RCT – start March 2015

**inclusion criteria**
- age > 65
- multiple cardiovascular RF or cardiovascular disease

**exclusion criteria**
- dementia
- computer illiteracy

- **Netherlands**
  - N = 2050

- **France**
  - N = 1100

- **Finland**
  - N = 1100

**Baseline assessment**

**central randomisation**

- **HATICE platform**
- **sham platform**

**18 months**

**Composite outcome: syst RR, LDL, BMI**
RCT – start March 2015

Netherlands N = 2050
France N = 1100
Finland N = 1100

Baseline assessment

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Composite outcome: syst RR, LDL, BMI

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• age > 65
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exclusion criteria
• dementia
• computer illiteracy

Secondary outcomes
• Individual risk factors
• cognitive decline
• incident cardiovascular disease
• mortality
• disability
• institutionalisation
acknowledgements

Academic Medical Center
Neurology and primary care
Pim van Gool
Eric Moll van Charante
Lisa Eurelings
Jan Willem van Dalen
Susan Jongstra
Cathrien Beishuizen
Suzanne Ligthart
Emma van Bussel
Tessa van Middelaar
Carin Miedema
Imke Hooijenga

Karolinska Institute
Miia Kivipelto
Francesca Mangialasche
Laura Fratiglioni

University of Eastern Finland
Hilkka Soininen
Mariagenese Barbera
Tiia Ngandu

University of Cambridge
Carol Brayne
Blossom Stephan

University of Toulouse
Sandrine Andrieu
Nicola Coley
Stéphany Savy

Vital health Software
Bram vd Groep

Novapten
Yannick Meiller
Juliette Guillemont

www.hatice.eu  www.edpi.org