Population screening and intervention for vascular disease in Danish men (VIVA): a randomized controlled trial

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Disclosure

Speaker name: Jes Lindholt

I have the following potential conflicts of interest to report:

☐ Consulting
☐ Employment in industry
☐ Stockholder of a healthcare company
☐ Owner of a healthcare company
☐ Other(s)

X I do not have any potential conflict of interest
Primary aim

Screening for CVD hasn´t caught much attention

Primary to test whether *triple Vascular screening* for AAA, PAD and hypertension reduces overall mortality in 65-74 year old men

Sample size calculation $\approx 50,000$

- RCT 1:1 based upon a relative risk reduction of 5%
- $2 \times 23,604 (\alpha=5\%, \beta=90\%)$
Secondary aims

• Many, but particular for health policy makers
  - Cost effectiveness
  - QoL consequences (EQ-5D)
  - Harms (diabetes, intracerebral haemorrhage, renal failure, cancer, and 30 d postoperative mortality after cardiovascular procedures)
Enrollment 2008-2011

- **Central Region of Denmark** – 1.2 million inhabitant (>1/5 of the Danish population)
- No exclusions: **All 50,168 men randomised**
- Computer-based randomisation secured concealment - stratified by the 16 municipalities
- The control group was masked
- Authors had no influence on- and were blinded for outcomes to date of analysis

Organisation

- at 14 local hospitals/Health centres
- by 6 special-trained nurses
- in 3 mobile teams
- Abdominal US and Doppler-based ABI (Pic) + consultations of positive findings + controls
- Assisted by a secretary
Interventions of positive findings

- Men with an AAA (+30 mm)
- Men with PAD (ABI < 0.90 or > 1.4)

Nurse driven consultation for confirmation and initiation of preventive actions
- 75 mg Low dose aspirin
- 40 mg Simvastatin
- Instructions on diet, smoking cessation, and exercise.

Men with suspected unknown moderate to severe hypertension (BP > 160/100 mmHG)

Referred for confirmation and treatment at G.P.

AAA < 5 cm
Annual US control

AAA +5 cm
CT scan and vascular evaluation

Interventions of positive findings

**Attendence rate:** 75%

**Prevalence of positive findings**

*Abdominal aortic aneurysm*
- 619 AAAs (3.3 %)
- 61 > 55 mm (10%)

307 (49.6%) had repair within five years.

*Peripheral arterial disease*
- 2,073 with PAD (11%)
- 1229 (60%) impaired walking

80 (4%) had repair for IC within five years.

*Possible hypertension*
- 1,963 (10%)

33% with AAA/PAD (4% of all) initiated statin and/or aspirin

Approx. 1/3 initiated treatment

## Baseline characteristics

### Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Invited group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69 (64-75)</td>
<td>69 (64-75)</td>
</tr>
<tr>
<td>Prescription medication during last year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombotic agents</td>
<td>7426 (30%)</td>
<td>7479 (30%)</td>
</tr>
<tr>
<td>Lipid modifying agents</td>
<td>8863 (35%)</td>
<td>8904 (36%)</td>
</tr>
<tr>
<td>Antihypertensives and beta blocking agents</td>
<td>5635 (22%)</td>
<td>5475 (22%)</td>
</tr>
<tr>
<td>Drugs used in diabetes</td>
<td>2534 (10%)</td>
<td>2445 (10%)</td>
</tr>
<tr>
<td>Hospital admission during last 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>760 (3%)</td>
<td>744 (3%)</td>
</tr>
<tr>
<td>AMI</td>
<td>650 (3%)</td>
<td>685 (3%)</td>
</tr>
<tr>
<td>Ischemic heart disease ex. AMI</td>
<td>1638 (7%)</td>
<td>1643 (7%)</td>
</tr>
<tr>
<td>Peripheral occlusive arterial disease</td>
<td>269 (1%)</td>
<td>247 (1%)</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>753 (3%)</td>
<td>734 (3%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>692 (3%)</td>
<td>718 (3%)</td>
</tr>
</tbody>
</table>

Data are n (%) or mean (range). AMI=acute myocardial infarction.
7% reduced overall mortality

No implemented population-based cancer screening programme has been able to demonstrate any effect on overall mortality

HR 0.93 (95% CI 0.88;0.98); p=0.012

Numbers needed to be invited (NNI): 169 (95% CI 89-1811).

Numbers needed to be screened to save one life within five years: 125
Cost effectiveness

- **Cost of screening:** €32 per invitee
  incl. the invitation procedure, transportation costs, utensils, overhead costs, 75% work load and equipment

- **Incremental cost of screening:** €148 (95% CI, -215 to 512) per invitee. incl. screening, medication, GP consultations, out-and in-hospital contacts (incl. CVD surgery)

**Costs of a LY and a QALY gain were respectively €6,872 and €2,148.**

- At a threshold for willingness to pay of €40 000, the probabilities for cost effectiveness were estimated at **98% and 99%**, respectively.

Initiation of preventive medication and AAA repair

**Antithrombotics**

- Invited group
- Control group

**Statins**

- Invited group
- Control group

**Antihypertensiva**

- Invited group
- Control group

**Elective AAA repairs**

- Proportion surgically repaired
No significant serious harms

Table 4: Adverse events

<table>
<thead>
<tr>
<th>Pharmacological therapy for diabetes</th>
<th>Control group</th>
<th>Invited group</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use initiated after baseline</td>
<td>91154</td>
<td>1376</td>
<td>92503</td>
</tr>
<tr>
<td>Any use</td>
<td>91525</td>
<td>3779</td>
<td>92836</td>
</tr>
<tr>
<td>Intracerebral haemorrhage</td>
<td>104028</td>
<td>146</td>
<td>105259</td>
</tr>
<tr>
<td>Renal failure</td>
<td>103006</td>
<td>668</td>
<td>104295</td>
</tr>
<tr>
<td>Cancer</td>
<td>9771</td>
<td>3637</td>
<td>99142</td>
</tr>
<tr>
<td>Death within 30 days after surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAA repair</td>
<td>104245</td>
<td>10</td>
<td>105448</td>
</tr>
<tr>
<td>PAD repair</td>
<td>104245</td>
<td>3</td>
<td>105448</td>
</tr>
<tr>
<td>CABG</td>
<td>104245</td>
<td>4</td>
<td>105448</td>
</tr>
<tr>
<td>PCI</td>
<td>104245</td>
<td>28</td>
<td>105448</td>
</tr>
<tr>
<td>Total</td>
<td>104245</td>
<td>41</td>
<td>105448</td>
</tr>
</tbody>
</table>

NA=not applicable, AAA=abdominal aortic aneurysm, PAD=peripheral artery disease, CABG=coronary artery bypass graft, PCI=percutaneous coronary intervention, CVD=cardiovascular disease.
### Consequences in Quality of life

<table>
<thead>
<tr>
<th>Baseline survey</th>
<th>Positive screening test</th>
<th>Followed after positive screening test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=1963)</td>
<td>PAD (n=1261/n=1306)</td>
</tr>
<tr>
<td></td>
<td>Mean  SD  P-value</td>
<td>Mean  SD  P-value</td>
</tr>
<tr>
<td>General index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attenders</td>
<td>0.891  0.001</td>
<td>0.823  0.182  &lt;0.001*</td>
</tr>
<tr>
<td>Controls</td>
<td>0.870  0.005</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>0.020  0.005  &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attenders</td>
<td>0.109  0.002</td>
<td>1.157  0.364  &lt;0.001*</td>
</tr>
<tr>
<td>Controls</td>
<td>0.121  0.011</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>-0.012  0.011</td>
<td></td>
</tr>
</tbody>
</table>

### Longitudinal survey

<table>
<thead>
<tr>
<th>PAD (n=1261/n=1306)</th>
<th>AAA (n=445/n=460)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean  SD  P-value</td>
<td>Mean  SD  P-value</td>
</tr>
<tr>
<td>General index</td>
<td></td>
</tr>
<tr>
<td>(n=1590)</td>
<td></td>
</tr>
<tr>
<td>Before screening</td>
<td>0.846  0.004  &lt;0.001</td>
</tr>
<tr>
<td>Before control</td>
<td>0.862  0.004</td>
</tr>
<tr>
<td>Difference</td>
<td>0.016  0.003</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td></td>
</tr>
<tr>
<td>(n=1648)</td>
<td></td>
</tr>
<tr>
<td>Before screening</td>
<td>0.142  0.009</td>
</tr>
<tr>
<td>Before control</td>
<td>0.127  0.008</td>
</tr>
<tr>
<td>Difference</td>
<td>0.015  0.063  0.063</td>
</tr>
</tbody>
</table>

PAD = Peripheral artery disease, AAA = abdominal aortic aneurysm, SD = standard deviation.
* = compared with attenders tested negative.

Overdiagnosing - not offered or do not accept prophylactic therapy causing net benefit in life expectancy

Of the 168 out of 169 invited men whose life will not be saved,
- 42 (25%) will decide not to participate in screening,
- 98 (58%) will be tested negative,
- 10 (6%) will be diagnosed and accept prophylactic therapy

18 (11%) will be potentially overdiagnosed

In breast cancer screening, between **19% and 57%** are estimated to be overdiagnosed

Ref. : Carter JL, Coletti RJ, Harris RP. Quantifying and monitoring overdiagnosis in cancer screening: a systematic review of methods. *Bmj* 2015; **350**: g7773

Overtreatment - undergoing treatment not causing a net benefit in life expectancy

10 out of the 169 men accepts prophylactic action,
- 1 out of the 2 (52%) who undergo surgery
- or 8 out of the 9 (88%) who are treated pharmacologically will be overtreated.

For comparison, 5-7 preventive carotid TEAs are needed to save one life from death or major stroke in patients with symptomatic carotid stenosis.

Vascular triple screening of 65-74 yr old men

- 7% lower overall mortality
- 169 NNI
- €2148 per gained QALY
- No serious negative side effects
  (Postop deaths, CNS bleeding, DM, cancer, uraemia, QoL, overdiagnosing & overtreatment)

For clinicians:
- AAA & PAD patients ought to receive statins & antiplatelets

For health policy makers:
- Implement triple vascular screening of 65-74 year old men
Thanks for the attention!

The VIVA screening trial team 2008