Preliminary Ten Year Results from a Randomised Single Centre Mass Screening Trial for Abdominal Aortic Aneurysm

J.S. Lindholt, S. Juul, H. Fasting and E.W. Henneberg

Vascular Research Unit, Department of Vascular Surgery, Viborg Hospital, Denmark, and Department of Epidemiology, Institute of Public Health, University of Aarhus, Denmark

Background. At present, several regions and countries are considering screening for abdominal aortic aneurysm (AAA). However, The Chichester Aneurysms Screening Trial has reported poor long term benefit of screening for AAA. We therefore supplement previously published data with a preliminary analysis of the ten-year mortality from AAA, based upon population-based data until 2002 (7 years) and incomplete hospital-based information on deaths until 2005 (10 years).

Methods and material. In 1994 we started a randomised screening trial of 12,639 64–73 year-old males; 6,306 were controls, and 6,333 were invited to an abdominal ultrasound scan at their district hospital. Information on all deaths until 15.3.2005 was obtained from the Office of Civil Registration. Information on AAA related deaths was obtained from the national registry of Causes of Deaths from 1.4.1994 to 31.12.2001, and supplemented with AAA deaths known to the Danish National Patient Registry until 15.3.2005. Operations were obtained from the Danish National Vascular Registry from 1.4.1994 to 15.3.2005.

Death certificates and medical records were reviewed by two independent assessors. The analyses were based on “intention to treat” from the date of randomisation.

Results. The attendance rate was 76.6% and 191 (4.0%) had an AAA. The median observation time was 9.58 years. In the invited group 13 subjects were acutely operated on compared to 40 in the control group (Risk ratio: 0.32 (95% C.I. 0.17–0.60, P < 0.001)), and 14 died due to AAA compared to 51 in the control group (Hazard ratio: 0.27 (95% C.I.: 0.15–0.49, P < 0.001).

Conclusion. Over ten years, screening reduced mortality from AAA by 73%, and the frequency of emergency operations by 68%.

Keywords: Randomised controlled trial; Mass screening; Abdominal aortic aneurysm; Costs; Benefits; Effectiveness.

Introduction

In spite of increased numbers of elective operations for abdominal aortic aneurysms (AAA), the sex- and age standardised mortality of ruptured AAA continued to increase. AAA seldom causes symptoms before rupture and when rupture occurs approximately 90% of patients die.1–5 This is in contrast to a mortality risk of 4–7% by elective aneurysmal resection. The presence of an asymptomatic phase which is easily detectable by ultrasound with a relatively low risk treatment compared to the lethality of ruptured AAA has stimulated research into the role of screening for AAA. Our Viborg study has demonstrated favourable benefits6 and cost effectiveness after five years.7 However, this is not the case in all studies.8,9 The ten year cost effectiveness analyses from the MASS trial9 and the Viborg Study6 were both theoretical, and were based upon conservative assumptions: for instance, we did not include potential additional saved lives after the observed five year period, only lives gained from 18 to 60 months. Furthermore, we used the observed difference in the AAA-specific mortality rates. This is probably an underestimation of the benefits, since the incidence of ruptured AAA increases with age.3

On the other hand, the frequency of non-compliance among cases with a conservatively treated AAA and cases unfit for surgery will probably also increase with age, and thus impair the effectiveness of screening. We therefore extended the analysis of the Viborg trial, with population-based data for the first seven
Material and Method

The study has been described in detail earlier. In brief, in 1994 we randomised all men living in Viborg County and born in 1921–1929. During 1995–1998 we randomised all of those who became 65 years old that year. The mean age at randomisation was 67.7 years (range 64.3 to 73.8 years) (Fig. 1).

After randomisation, 6306 were controls, while 6333 were invited to an abdominal ultrasound scan at their district hospital by a mobile screening team. Non-responders were reinvited once. An AAA was defined as a maximal infrarenal aortic diameter of 3 cm or more. Men with an AAA of 5 cm or more were referred to a vascular surgeon. The remaining AAA-patients were offered yearly follow-up examinations, to check for any expansion. After three to five years, 248 men with an initially ectatic aorta were offered rescreening.

Randomisation took place in blocks of approx. 1000 persons to avoid long delay between randomisation and invitation to screening. Included men were randomly assigned in a proportion 1:1 to be invited to screening or to be controls. No exclusions were made. The allocation schedule was performed by use of Epi Info version 6.

Outcome measures

Primary outcome measures were elective and acute operations, and deaths caused by AAA from the time of randomisation to 15.3.2005. Operations for AAA were identified in the national vascular registry “Karbasen” (www.karbase.dk). The patient records were used to record indication, operation time, and hospital course. In other respects, the operations were based on hospital records for the 3 years following the randomisation.

Fig. 1. Flow-chart concerning screening for abdominal aortic aneurysm.
number of preoperative blood transfusions, type of graft, and complications. Medical and surgical complications were acute myocardial infarction, cardiac failure, severe pulmonary complications requiring treatment, artificial ventilation for more than 48 hours, dialysis, intensive unit stay for more than 72 hours, stroke, arrhythmia, wound complications including rupture, operation due to bleeding, ileus, operation due to intestinal ischemia, thrombosis and peripheral embolisation requiring operation.

Information on all deaths until 15.3.2005 was obtained from the Office of Civil Registration. AAA as primary or contributing cause of death was identified in the national Registry of Causes of Death concerning deaths taking place from April 1994 to December 2001. Causes of deaths outside hospitals were unknown in the last period from 2002 to 2005. Consequently, we obtained nation wide information on hospital diagnoses of ruptured AAA from January 2002 until March 2005 by the National Patient Registry, and AAA-related deaths after surgery as deaths happening within 30 days after operation for AAA.

Patient records and death certificates on men with AAA as primary or contributing cause of death and unoperated cases of ruptured AAA who died within the admission were reviewed by two independent vascular surgeons. They were blinded to the randomisation group and to each other’s evaluations, and each assessed the deaths to be certainly, possibly or not caused by AAA. Cases where both assessors evaluated the death to be certainly or possibly caused by AAA were classified as AAA deaths. No efforts were made to obtain agreement.

A cost effectiveness estimate of costs per saved life was done by using the previously reported costs for screening and surveillance, which were prospectively recorded during the first year of the trial. The data obtained were salaries and travel reimbursement (for doctor and nurse), stamps, envelopes, printing costs of invitations, laptop computer, and various products such as ultrasound gel.

To assign costs of hospitalization for surgery, the costs calculated for planned and emergency procedures in the MASS trial were used. The costs were not discounted, and indirect costs for the attenders were not included.

**Statistical analyses**

Risk ratios of operation for AAA and AAA-specific deaths between the invited and the control group were estimated by Cox regression. The analyses were calculated on the basis of “intention to screen”, from the date of randomisation to death (or operation) or 15.03.2005.

Concerning operative characteristics, comparison of proportions between the invited and the controls was performed by Fisher’s exact test and odds ratios were calculated. Comparison of means between the invited and the controls were performed by Wilcoxon’s rank sum tests due to non-normal distributions and unequal variances. SPSS and PEPI were used as software for the analyses. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Ethics**

The trial was approved by the regional scientific ethics committee and by the national data protection authorities.

The authors have no potential conflicts of interests.

In accordance with the Clinical Trial Registration Statement from the International Committee of Medical Journal Editors, the trial is registered at clinical trials with the registration number ISRCTN65822028.

**Results**

As mentioned, 12,639 men were included with a mean age of 67.7 years. The median follow up time was 9.6 years (25–75 percentiles: 6.6–10.6 years). No differences in observation length and age at inclusion were observed between the invited group and the control group.

The attendance rate was 76.6% (95% CI: 75.6%–77.7%). Of the 4,852 attenders, 4816 had visible aortas, 191 (4.0%; 95% CI: 3.4%–4.6%) had an AAA at the initial examination.

Operations

Twenty-four of the screened men (0.5%; 95% CI: 0.3%–0.7%) had an AAA above 5 cm in diameter at the initial screening scan, and were referred for surgery. During the following years another 48 men were referred for elective surgery due to expansion (Fig. 1). There were 76 planned operations in the invited group compared to 29 in the control group (Risk ratio: 2.56; 95% C.I.: 1.67–3.93, $P = 0.002$) (Table 1).

Elective AAA operations among men diagnosed by screening compared to other elective AAA operations were characterised by significantly fewer perioperative blood transfusions, shorter operation time and an insignificant tendency to fewer complications.
perhaps partly due to an insignificantly higher proportion of tube grafts used in the invited group (58% vs 48%). However, the invited men did not have shorter hospital stays (11.3 versus 11.4 days) (Table 2 and 3).

A total of 13 emergency procedures were performed in the invited group compared to 40 in the control group (Risk ratio: 0.32 (95% C.I. 0.17–0.60, P < 0.001)), corresponding to 68% fewer emergency procedures (Fig. 2). The total number of operations was increased by 29% in the invited group corresponding to four additional operations per year among the approx. 230,000 inhabitants in Viborg County if the screening offer became permanent.

Fig. 2 shows that the operative activity seems to have been steady over the observation period after an initial peak in the screening group of planned procedures.

Mortality

Concerning planned operations, three men died within 30 days postoperatively (3.0%; 95% C.I.: 0.6–8.6%), and a fourth died 2½ months after the operation due to operative complications. The 30 day postoperative mortality after emergency operations without rupture was 33.3% (95% C.I.: 9.9–65.1%) and with rupture 58.5% (95% C.I.: 42.1–73.7%).

Table 4 and Fig. 3 shows the mortality of AAA related deaths including the late postoperative death. There were a total of 14 AAA deaths in the invited group compared to 51 in the control group. Thus, screening reduced deaths caused by AAA by 73% (Hazard ratio: 0.27 (95% C.I.: 0.15–0.49, P < 0.001) (Fig. 3).

During 1994 to 2001 we recorded 48 AAA deaths from the population-based Register of Causes of Death. From the hospital-based information we identified 31 AAA deaths, corresponding to a reporting of 65% of all AAA related deaths. However, in the hospital-based data we found a similar relative risk (0.45 (95% CI: 0.23–0.86)) as in the population-based data (0.37 (0.21–0.67)).

Fig. 4 shows the mortality from all causes. There were 2,184 deaths in the invited group compared to 2,234 in the control group (Hazard ratio: 0.97; 95% C.I.: 0.91–1.03).

Table 5 shows the costs per prevented death calculated to be Euro 2,301 (£1,587).

Discussion

During a 10 year period, screening for AAA in Viborg County reduced the average frequency of emergency operations by 68%, and mortality from AAA by 73% by performing 29% more AAA operations.

AAA-specific and overall mortality

In the only randomised screening trial reporting long term results, the Chichester AAA screening trial found the benefit of screening peaked around the fifth year and there was only a 21% lower AAA mortality after 10 years.11 This is in contrast to our findings. The authors suggested AAA-related deaths among non-attenders, increasing non compliance for surveillance and increasing frequency of contraindications for surgery as possible explanations. Such problems seem not to dominate in the Viborg trial, since Fig. 2A shows a steady activity of preventive operations throughout the observation period in the invited group - however, perhaps with a tendency to fade out after 8–10 years. The difference between the two studies may be age dependent; the Viborg Study, only recruited 64–73 year old men and added the new 65 years old men the following 4 years, while the Chichester study recruited 65–80 year old men.12

We could not find any sign of reduced overall mortality by screening, but as in the MASS trial11 a trend was noticed after five years, so the analysis was repeated after ten years, and the trend had disappeared.
We have earlier reported that operations for screen-detected AAA had less complications compared non-screen-detected AAA. Later, the permanent Gloucester screening program reported lower mortality of operations of screen-detected AAA. Both findings may be due to selection, and perhaps also to earlier surgery in screen detected cases with consequently more fit patients.

The present study demonstrates that the planned operations in the screening group were shorter, required less transfusion and were more likely to employ an aortic tube. These factors are associated with fewer complications - but the frequency of complications was not lower than in the control group. However, a trend was noticed, and it seems likely that screening may reduce complications and perioperative mortality in the long run. In the large randomised multicentre aneurysm screening study (MASS), the perioperative mortality in the screening group was 5% compared to 10% in the control group (a non-significant difference).

A remarkable low price per prevented death was noticed. The explanation is the relatively high reduction in AAA related mortality combined with a strong shift in the indications of surgery. The method does not follow the international guidelines for such studies. Among others, costs and effects of screening are not discounted, which introduces a bias. In the MASS trial, however, discounting actually produced a lower cost difference between the two groups. Furthermore, saved living years were not calculated due to the lack of causes of deaths outside hospitals. This lack of data must be expected to have increased the costs per saved life since the number of saved lives must be expected to be underestimated.

The British costs for surgery were chosen because it includes additional hospital costs after discharge from the hospital. It could be questioned whether the British costs of surgery can be generalised to Denmark. The costs of planned operations compares very well with the existing Diagnosis Related Group (DRG) costs in Denmark at the moment, but not with the

### Table 3. Characteristics of operations for asymptomatic abdominal aortic aneurysms classified according to offer of screening

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean (SD)</th>
<th>(25) Median</th>
<th>(75) Percentiles</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation-time (min)</td>
<td>Controls 29</td>
<td>170.7 (66.6)</td>
<td>(123)</td>
<td>(210)</td>
<td>0.043</td>
</tr>
<tr>
<td></td>
<td>Invited 76</td>
<td>139.7 (42.5)</td>
<td>(120)</td>
<td>(159)</td>
<td></td>
</tr>
<tr>
<td>Number of blood transfusions</td>
<td>Controls 29</td>
<td>2.34 (3.84)</td>
<td>(0) 1 (3)</td>
<td></td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>Invited 76</td>
<td>0.88 (1.39)</td>
<td>(0) 0 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission time (days)</td>
<td>Controls 29</td>
<td>11.3 (6.07)</td>
<td>(7) 8 (14)</td>
<td></td>
<td>0.989</td>
</tr>
<tr>
<td></td>
<td>Invited 76</td>
<td>11.4 (9.09)</td>
<td>(7) 9 (11)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-values by Wilcoxon rank sum test.

### Operative complications

### Cost effectiveness analysis

Fig. 2. A–B. Surgical consequences of screening for abdominal aortic aneurysms concerning planned and emergency operations for abdominal aortic aneurysms.

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costs of emergency operations which seem higher than in the MASS trial. The DRG costs are the mean hospital costs for the treatment of a patient with a specific diagnosis. These are based on independent cost studies from different hospitals in Denmark.

**Potential bias**

Our study groups had similar age distributions and average times at risk. The analysis was carried out according to the intention to screen principle, and we have no reason to suspect confounding. No doubt there is an under-reporting of AAA deaths during the last part of the follow-up period where only hospital deaths were recorded. We find, however, no reason to believe that this under-reporting was different in the intervention and control group, and the experience from the first part of the study period when AAA-related mortality from hospital-based and population-based information could be compared, supports this assumption.

It is possible that some deaths may have been misclassified as due to abdominal aortic aneurysm, as autopsy seldom is carried out. However, 53% of the patients dying of AAA underwent surgery and 80% died at hospital providing valid data for evaluation. Consequently, the two vascular surgeons disagreed on only four cases of death from hospital and autopsy reports. The assessors were blinded to group allocation, and we conclude that classification bias seems unlikely.

**Conclusions**

In all, screening increased the number of planned operations 2½ times over a ten year period in Viborg County. Despite less need for blood transfusions and shorter operation times among elective operated cases in the invited group compared to the control group, the frequency of complications and the admission time were not lower in the invited group compared to the controls.

Screening reduced the number of emergency operations by 68%, and the net result was only 29% extra

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**Table 4. Deaths from abdominal aortic aneurysms classified according to indication and attendance to screening**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Invited</th>
<th>Non-attenders</th>
<th>Attenders</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outside hospital</td>
<td>15</td>
<td>2</td>
<td>2</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Unoperated at</td>
<td>13</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Planned</td>
<td>1</td>
<td>3</td>
<td></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Emergency, -</td>
<td>4</td>
<td></td>
<td></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Emergency, +</td>
<td>18</td>
<td>6</td>
<td>3</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>14</td>
<td>4</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

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**Fig. 3. AAA specific mortality in men invited to screening or being controls.**

**Fig. 4. Total mortality in the invited and control group, respectively.**

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Table 5. Cost effectiveness estimation of screening for abdominal aortic aneurysms

<table>
<thead>
<tr>
<th>Activitét</th>
<th>Price per unit (Dkr)</th>
<th>Invited group</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Dkr</td>
<td>N</td>
</tr>
<tr>
<td>Initial screening</td>
<td>83.75</td>
<td>4,852</td>
<td>405,601</td>
</tr>
<tr>
<td>Recall scans</td>
<td>83.75</td>
<td>845</td>
<td>70,768</td>
</tr>
<tr>
<td>Re-screening</td>
<td>83.75</td>
<td>248</td>
<td>20,770</td>
</tr>
<tr>
<td>Admissions for planned operations*</td>
<td>80,420</td>
<td>76</td>
<td>6,111,920</td>
</tr>
<tr>
<td>Admissions for emergency operations*</td>
<td>130,089</td>
<td>13</td>
<td>1,691,157</td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
<td>8,300,021</td>
<td>69</td>
</tr>
<tr>
<td>Difference (Dkr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference (£)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference (Euro)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costs per saved life (DKr)</td>
<td>102.588</td>
<td>405,601</td>
<td>2,332,180</td>
</tr>
<tr>
<td>Costs per saved life (£)</td>
<td>70.767</td>
<td>70,767</td>
<td>20,656</td>
</tr>
<tr>
<td>Costs per saved life (Euro)</td>
<td>2,773</td>
<td>2,773</td>
<td></td>
</tr>
</tbody>
</table>

Exchange rates from The National Danish Bank the 1st of June, 2006: 1£ = 10.80 Dkr and 1 Euro = 7.45 Dkr.
* Based upon results from the MASS trial (BMJ 2002;325:1135-1141).

operations, and 73% lower mortality of AAA over a ten year period in the invited group compared to the control group. The costs per saved life were estimated to be 2,773 Euros.

The study supports a substantial long term benefit of screening for AAA.

Acknowledgements

The vascular surgeons, Jes Sandermann and Franz von Jessen, are thanked for their independent review of autopsy and hospital reports and judgements concerning classification of cause of death. Anette Sahlholdt, Sten Vammen, Henriette Lindholt, and Jette Støvring are thanked for assistance concerning data collection.

The Health Department of Viborg County, The Danish Heart Foundation, The Danish National Council of Health Research, The Foundation of Research in Western Denmark, The Health Department of Viborg County, The Danish Heart Foundation, The Danish National Council of Health Research, The Foundation of Research in Western Denmark, and The Foundation of Rosa and Asta Jensen are thanked for economical support.

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Accepted 13 June 2006
Available online 8 August 2006