Abdominal aortic aneurysms

Screening and prognosis

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The present thesis is based on the following published papers, which will be referred to in the text by their Roman numerals:

I. Lindholt JS, Juul S, Fasting H, Henneberg EW. Screening for AAA: single centre randomised controlled trial. BMJ 2005;330:750-754.

II. Lindholt JS, Juul S, Henneberg EW. High-risk and Low-risk Screening for AAA Both Reduce Aneurysm-related Mortality. A Stratified Analysis from a Single-centre Randomised Screening Trial. Eur J Vasc Endovasc Surg. 2007;34:53-8.

III. Lindholt JS, Sørensen J, Søgaard R, Henneberg EW. Benefit and cost effectiveness analysis of screening for AAA based on 14 years results from a single-centre randomised controlled trial. Br J Surg 2010; accepted

IV: Lindholt JS. Aneurysmal wall calcification predicts natural history of small AAA. Atherosclerosis 2008; 197;673-678

V. Lindholt JS, Jorgensen B, Shi GP, Henneberg EW. Relationships between activators and inhibitors of plasminogen, and the progression of small AAA. Eur J Vasc Endovasc Surg. 2003;25:546-51.

VI: Lindholt JS, Stovring J, Ostergaard L, Urbonavicius S, Henneberg EW, Honore
B, Vorum H. Serum antibodies against Chlamydia pneumoniae outer membrane protein cross-react with the heavy chain of immunoglobulin in the wall of abdominal aortic aneurysms. Circulation. 2004;109:2097-102

VII: Lindholt JS. Relatively high pulmonary and cardiovascular mortality rates in screening-detected aneurysmal patients without previous hospital admissions.
Eur J Vasc Endovasc Surg. 2007;33:94-9.

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HISTORIC VIEW OF THE MANAGEMENT OF AAA

One could say that abdominal aortic aneurysm (AAA) surgery began with the first attempts to control bleeding vessels by ligation. The great surgeon of ancient India, Sushruta (approx. 800-600 BC), was the first to ligate bleeding vessels with hemp fibres[2]. However, Antyllus, a second-century surgeon from ancient Greece, was the first to describe the anatomy and treatment of aneurysms. He described two sorts of aneurysmal lesions: those originating from a local arterial dilatation, which were cylindrical, and those arising from trauma, which were rounded. He precisely described proximal and distal ligation and even evacuation of the aneurismal sac[3], a technique which was to be forgotten for 17 centuries until Astley Cooper in 1817 ligated the aortic bifurcation in a 38-year-old man named Charles Hudson due to a ruptured iliac aneurysm. Cooper knew the presence of the aneurysm and described it as having been steadily increasing during the last year and doubled in size 3 days before surgery. Shortly after admission, the aneurysm ruptured through the skin. Cooper made a transperitoneal incision and placed a silk ligature just above the aortic bifurcation, while Hudson was still in bed. Hudson appeared remarkably well the following day, but died 40 hours postoperatively[4]. More than 100 years later, Rudolph Matas performed the first successful ligation of the aorta in April 1923. The patient was a 28-year-old woman with a ruptured syphilitic aneurysm at the aortic bifurcation. She survived and lived 17 months before dying of tuberculosis[5]. Nevertheless, ligation never became a gold standard of treatment due to discouraging results.

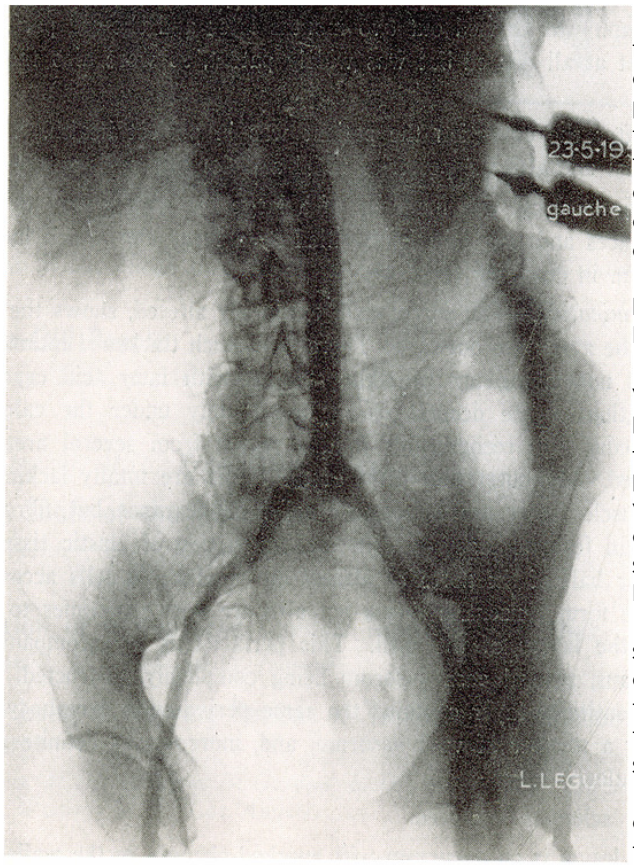


Figure 1. Postoperative arteriography of the first AAA resection and vascular reconstruction performed by Dubost[9]

In 1944, Clarence Crafford from Sweden resected an aortic coarctation in a 12-year-old boy and in a 37-year-old man. In both cases, the aorta was repaired with an end-to-end anastomosis, and both patients recovered well. Reestablishment of the aortic circulation in humans had now been proven feasible, and the next mountain to climb was to bridge large gaps of aorta[6].

In 1948, Gross showed the way by using small preserved arterial grafts in humans with aortic coarctation, but the real breakthrough happened in Paris in November 1950, where Jacques Oudot replaced an occluded aortic bifurcation. He used an aortic allograft from a young victim of an accident. Persistent ischemia of the right leg forced him to place a second homograft from the left to the right external iliac artery. Hereafter, the patient recovered well[7]. Such a breakthrough had to be performed by a person with a highly developed sense of adventure, and indeed Oudot was an adventurer; some months before the operation, he participated in the first Ascent of Annapurna in the Himalayas. During the course of this expedition, he experimented with intra-arterial injections of vasodilatators to treat frostbite. Unfortunately, he died in 1953 after a fatal crash in his highly powered sports car on his way to skiing in Chamonix, only 40 years old[8].

Probably inspired by this first aortobiiliac bypass, the first repair of an AAA was also performed in Paris shortly after. In March 1951, Charles Dubost used a 14-cm-long preserved thoracic aorta from a young accident victim to replace an AAA in a 50 year-old man. Through a thoracoabdominal incision, the homograft was anastomosed to the aorta and the right common iliac artery, and the left common iliac artery was anastomosed end-to-side to the homograft[9] [Figure 1]. The patient survived and lived for another 8 years before dying of myocardial infarction in his home in Brittany.

Dubost was a pioneer in several fields; the same year he attempted the first renal transplantation – probably without consent from the donor of the kidney - a just guillotined criminal! He encouraged one of his pupils, Alain Carpentier, to develop a prosthetic heart valve, and in 1968 Carpentier implanted the first artificial heart valve in humans at his institution. The same year, Dubost successfully performed the first European heart transplantation[8].

Dubost´s operation in 1951 chocked the vascular surgical world, and prominent surgeons like DeBakey and Szilagyi rapidly adapted the procedure. However, the enthusiasm of homografts disappeared rapidly due to degenerative changes which made many of them short-lived.

From 1948, Arthur Voorhees was donated vinoyn-N cloths for parachutes from the US Air Force to explore the potential of using artificial grafts in animals. However, in 1952 an elderly man was admitted to the Columbia Hospital in New York with a ruptured AAA. The artery bank in New York was empty, so Voorhees rushed to his laboratory one floor above the operation theatre and constructed a tube graft of vinoyn-N on his sewing machine, autoclaved it and made a successful implantation. Unfortunately, the patient died postoperatively due to myocardial infarction, but stimulated by the initial success, the group started electively to implant vinoyn-N tubes in humans[10]. In 1954, the group published relatively attractive outcomes of 17 AAA resections in humans with implantation of vinoyn-N tubes [11].

One of the first patients being offered such repair of an AAA was the famous Nobel-prize taker from 1921, Professor Albert Einstein. Unfortunately, he considered the operative risk to be too high, and died in New York of ruptured AAA in 1955[12]. Rapidly, the procedure dispersed world wide, and the first reported operation for AAA was performed in Denmark in 1961[13].

In 1970, Charles de Gaulle died due to sudden rupture of an unknown AAA. This risk of rupture without warning symptoms, and the development of portable ultrasonographic equipment stimulated in 1984 Alan Scott in the South of England to explore the potential benefits of screening for AAAs[14]. About twenty years later the definitive evidence of benefit was reported by him and his colleagues in the randomised Multicentre Aneurysms Screening Study [MASS][15] followed by a recommendation for nation-wide screening in the UK by the National Screening Committee in 2006. In

Denmark, a population screening trial for AAAs started in Viborg in 1994[16][I].

The next breakthrough in the battle against AAAs happened in 1990. After successful animal experiments, Juan Parodi attempted endovascular repair of a human AAA in Buenos Aires using a hand-made tube graft[17].

In Denmark, the first reported endovascular prosthesis was implanted in 1996 in Viborg[18].

In 1999, the first fenestrated endograft was used to seal a proximal endoleak[19]. Even today, the use of endovascular repair remains controversial because the ends of the stent cannot be securely anchored to the aortic wall and are thus at risk of leaking with renewed risk of rupture. However, in 2005 the first endostapling graft was implanted by Takoa Ohki. It holds the potential to revolutionize endovascular procedures.

It is difficult to believe that new surgical techniques for treatment of AAAs will be developed, and future breakthroughs must be expected to lie in the development of efficient medical or genetic treatment[20-23].

INTRODUCTION AND SPECIFIC MAJOR AIMS OF THE THESIS

Despite of the development of an operative treatment option and improved safety of elective operations, the incidence and mortality of AAAs has risen continuously since Dubost made the first successful resection. This development combined with the possibility of making a reliable and inexpensive diagnosis has stimulated a debate as to whether screening for AAAs should be recommended or not. The WHO formulated screening criteria back in 1968[24]. Over time, these proved insufficient. The criteria were expanded by the Council of Europe in 1987[25], and by a working group of The Danish National Board of Health in 1990[26] [Table 1].

Consequently, a Danish randomised screening trial was initiated in 1994 to explore whether screening for AAA meets these criteria.

Part I of this thesis reviews the existing knowledge at time of initiating the screening trial according to these criteria as by specification of the disease, reconsideration of the existing treatment strategies, and considerations of a screening programme as suggested by the Council of Europe[25]. At present, a popular method to do this wpuld be as an HTA. However, this is not the approach the Danish Natrional Board of Health recommends for such pupose[26].

In addition, most AAA diagnosed by screening is too small initially to be recommended for operation, but a considerable proportion expands further and requires later surgery. This growth phase makes the AAAs a unique object for pathogenetic analysis of their progression and holds a key for potential medical intervention. Therefore Part II reviews potential risk markers of further expansion.

Based upon these reviews, identified lacks of knowledge are condensated in Part III, together with the specific major aims of the present work in this phesis, which were planned to be:

1. To determine the feasibility of a Danish hospital based screening programme of 64-73 year old men, their attendance proportion to screening, the prevalence and incidence of asymptomatic AAA, and the potential need for interval screening. The incidence of ruptured AAA and AAA-related mortality in Danish men aged 64-73, and in particular to analyse whether hospital-based mass screening for AAA reduces AAA related mortality after five years.

2. To assess risk factors for AAA and perform a stratified analysis in the above mentioned randomised population screening trial for AAA in men, with or without hospital diagnoses of chronic obstructive pulmonary disease (COPD) or cardiovascular disease, in order to evaluate whether the offer of screening is acceptable to those at high risk of having an AAA, and to evaluate whether the offer of screening may be restricted to such men in high risk.

3. To perform a long term analysis of whether hospital-based mass screening of Danish men aged 64-73 for AAA, reduces AAA related mortality and overall mortality after fourteen years. In addition, to estimate the long term cost effectiveness of such screening for AAA in Viborg County.

4. To investigate whether the degree of AAA-wall calcification judged by ultrasonography is associated with the aneurysmal growth rate and whether calcification is associated with later surgery. In addition, to examine whether such calcification is associated with future cardiovascular events and death.

5. To study the potential pathways in the plasmin activation associated with the progression of AAA, and the potential roles of smoking, homocysteine, Serum IgA-antibodies against Chlamydia pneumoniae (IgA-CP), Macrophage inhibiting factor (MaIF), and Tumor growth factor beta-1 (TGF-Beta-1) in these pathways. In addition, to correlate aneurismal progression with smoking and hyperhomocysteine, as this could reveal potential inhibition of aneurismal progression through smoking cessation and vitamin supplies.

6. To detect outer membrane protein (OMP) from Chlamydia pneumoniae in AAA wall tissue by use of antibodies against OMP from Chlamydia pneumoniae purified from AAA patients and to search for potential cross-reacting proteins in the wall of AAAs. In order to identify possible causative agents, which could be treated, and thereby inhibiting further aneurysmal growth.

7. To analyse whether men with AAA not previously hospitalised with cardiovascular disease or COPD have higher mortality due to these disorders and therefore may benefit from preventive actions.

In part IV, the methods and materials used in the seven studies to cover these specific aims are described in Part IV.

In part V, the results of the studies are presented and discussed. Finally, conclusions are summarised in Part VI.

Table 1. Summary of the Danish criteria for advocating a nationwide screening programme [24-26]

1. The disease must be a major health problem.
2. The course of the disease without treatment must be sufficiently known.
3. The indication for treatment must be clearly defined.
4. The disease must be able to be diagnosed in asymptomatic or early symptomatic stages.
5. A suitable method for screening must be available.
6. The method must be evaluated concerning the validity, efficacy and predictive value.
7. The method must be acceptable for the population.
8. Ethical, psychological and stigmatising consequences must be evaluated.
9. The treatment of the diagnosed disease must be acceptable.
10. The benefits must be in reasonable proportion to the total costs.
11. The economic consequences must be evaluated as follows:
- Cost-benefit, cost-effectiveness, or cost-utility analysis.
- Changes in different health budget costs.
- Marginal economic consequences.
12. The screening effort must continue and not only be a one-off process.
13. Facilities for diagnosing and treatment must be available.
14. A detailed description must be presented concerning:
- Organisation.
- Management and Administration.
- System to record relevant data to ensure follow-up
- Plan for further referral and order of priority of positive findings.
- Information to the target group.
- Education and training of personnel.
- Execution of the test result

PART I. BACKGROUND

The Council of Europe published in 1987 guidelines for evaluation of potential areas of screening[25]. Guidelines, which later also were recommended further by a working group of The Danish National Board of Health [Table 1][26]. Initially, the problem must be defined by specification of the disease, trends concerning prevalence [Def.: proportion of the disease[27]], the incidence [Def.: new cases per observation time unit[27]], and consequences for the individual and the society.

1.1. DEFINITION OF SCREENING

By screening, the body is from a biological point of view examined for something abnormal, which the person do not suspect or have reacted upon. It may be an early phase of a disease, a prephase of a disease, or a risk factor of a disease [Def.: Characteristic that is associated with an increased risk of becoming diseased[27]]

From a technical point of view, screening may be wide, as the surveillance programs for pregnancies searching for individuals in particular risk, or specific as screening for breastcancer. The purpose of screening may be to protect the individual, other persons [as screening of blood for donations], society (as driving license renewal) or for saving money (as health screening before a life insurance can be signed).

Screening for AAA is specific, and seaks to identify an asymptomatic phase of the disease, in order to protect the individual.

1.2. DEFINITIONS AND SUBGROUPS OF AAA

An AAA is a dilatation of the abdominal part of the aorta, but no exact definition is available (Figure 2). In order to allow for normal biological variation, Scandinavian studies have defined an AAA as an anatomical abnormality where the ratio between the maximal AAA diameter divided by the supraaneurysmal aortic diameter reaches 1.5.[28-31]. This is a time-consuming definition for screening purposes, and the proximal part of the aorta may be located at a deep level which will produce higher variability of ultrasonographic measurements. Moreover, the size of the supra-aneurysmal diameter depends on whether it measured proximal or distal to the renal arteries, the neck of the AAA may hide a normal aorta, and two measurements which each produce variability will increase the overall variability[32-34]. Most studies therefore use a pragmatic definition as the criterion for an AAA: a maximal infrarenal aortic diameter of 30 mm or more and aortic diameters of 25-29 mm are described as ectatic or pre-aneurysmal dilatations.

AAAs may be divided by their localisation and their anatomical extension into abdominal and thoracoabdominal aneurysms[35]. AAAs located purely in the abdomen are classified according to their association with the renal arteries as infrarenal, pararenal with involvement of one or both renal arteries[36], or suprarenal[35].

The by far most common aortic aneurysms are the infrarenal aneurysms, as shown in Figure 1. At present, only infrarenal AAAs are considered for screening. They are further divided into juxtarenal aneurysms if there is no normal aorta below the renal arteries, and aortoiliac aneurysms if they extend into one or both iliac arteries[37]. This classification is important for the method of treatment and the risk involved in the treatment.

Infrarenal AAAs may also be divided into non-inflammatory, inflammatory [4-5%] or mycotic AAAs [1-2%][38;39].

The diagnosis by ultrasonographic scanning (US) and treatment does not differentiate according to this classification.

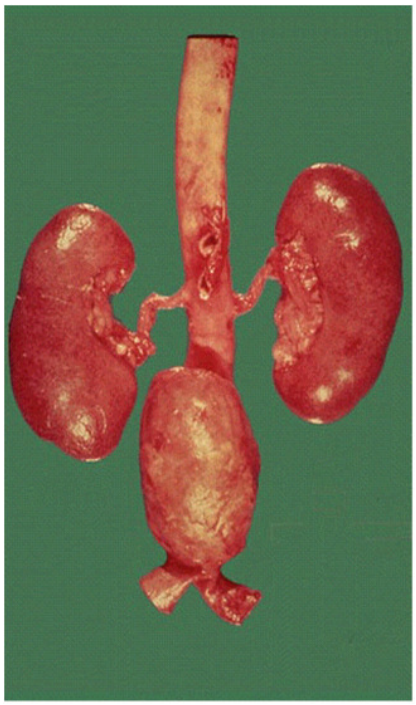


Figure.2. A small AAA starting below the origin of the renal arteries and ending just above the aortic bifurcation

1.3. SPECIFICATION OF THE DISEASE – A MAJOR HEALTH PROBLEM ?

1.3.1. Prevalence and incidence

Screening studies have shown an AAA prevalence of 4-10% among screened or autopsied men over 60 years increasing with age, whereas the prevalence in women was approximately 1-2%[40-44]. Furthermore, population-based studies have shown an annual increase in the prevalence of unruptured as well as ruptured AAAs of 4-12%. In some studies the relative increase was highest in women[45-53].

In all, the prevalence of AAA seemed to vary considerably from region to region, and was unknown in Denmark, until the start of the present Viborg Screening Study.

1.3.2. Consequences for the individual and the society.

1.3.2.1 Mortality

The incidence of AAAs and ruptured AAAs is increasing in the UK, Western Australia, Sweden, and The Netherlands. At present, 1-3% of the deaths of males between 65 and 80 years are caused by ruptured AAAs in the above-mentioned countries compared with 1.3% in Denmark[45-49;52;54-63] [Table 2].

Indications of a similar tendency in Denmark seems present; the number of AAA-related deaths in Denmark rose by 92% from 225 in 1980 to 433 in 1996[61-63].

By linear regression analysis, this increase is approx. 11 per year among males and 4.5 among females. The increase is not only due to an altered age distribution because the increase in the age-standardised mortality of AAAs in males in Denmark was 82% from 1980 to 1996[63].

In all, 60% of all AAA-related deaths and 86% of all AAA-related deaths among males occur among men aged 65 years or more. However, the registration of causes of death is encumbered with uncertainty caused by inconsistent coding and the obvious risk of misclassification. A risk of underreporting exists due to the known, high frequency of coexisting ischemic heart disease (IHD) which implies a logical risk of sudden death due to RAAA to become classified as death caused by IHD with consequently no autopsy been done afterwards. However, in Western Australia only 5% of the total amount of deaths caused by ruptured AAA were unexpected, which suggests that the proportion of diagnosed ruptured AAA may be surprisingly high[47;50].

1.3.2.2. Operations in Denmark 1983-2004

The number of operations for AAAs in Denmark increased from 235 in 1983[63;66] to 689 in 1997. It then dropped to 599 in 1999[67] but continued to increase after the millennium reaching 712 in 2004 (Figure 3). The decrease at the end of the last millennium could have been explained by the reports of level 1 evidence justfying a more restrictive indication for operation for asymptomatic AAAs[68;69], but these reports ought not influence the pattern of acute operations due to ruptured AAAs. Furthermore, the incidence of emergency operations without rupture declined from the mid nineties (1996-2004: Rho=- 0.78, P=0,001)[70].

This could be due to a report from Cambria et al in 1994 which showed that operation within 4 hours when an obvious rupture was not present was associated with an increased risk of death compared with delayed procedures[71]. In all, the overall incidence of such surgery increased from 46 to 132 per million per year from 1983 to 2004 (Rho=0.64, P=0.023). The incidence of planned operations rose from 20 to 63 per million per year from 1983 to 2004 (Rho=0.75, P=0.002). In spite of this increase in preventive operations, the incidence of operations for ruptured AAAs rose from 6 to 48 per million per year from 1983 to 2004 (Rho=0.59, P=0.049).

From 1996 to 2004, the mean annual incidence of elective operations was 22% higher in Danish counties with their own vascular surgical service compared with counties without such service[70].

The female/male ratio is unchanged: 1:6 for elective operations, 1:5 for symptomatic operations, and 1:10 for operations because of rupture. Despite an increase in the number of elective operations from 102 to 205, the proportion of elective operations has not increased significantly (from 43% to 49% (Chi sq.: P=0.15)).

Mortality by autopsy	Age					
	55 -59	60-64	65-69	70-74	75-79	80+
Malmö 1958-86(46)		16		56		113
England & Wales 1950-84(49)		22		66		119
Western Australia 1980-88(50)	12	21	44	91	100	169
Stockholm 1980-85(54)*		11		37		65
Chichester 1989(64)			82		198	
Worthing 1979-84(55)		27		106		125
Huntingdon 1991-95(65)*			54			
Denmark 1991(63)*	7	22	42	69	99	102

Table 2. Population-based studies of the male mortality rates of AAA per 100,000 years
***: Based on data from the National Registry of Causes of Death**

1.4. THE COURSE OF THE DISEASE WITHOUT TREATMENT

Disease prognosis can be described for either the clinical course or the natural history of illness. The term clinical course has been used to describe the evolution/prognosis of a disease that has come into medical care and is treated in ways that might affect the subsequent course of events. The prognosis of disease without medical intervention is termed the natural history of disease[27]. Only the clinical course of AAA is known – including the course without operative repair. However, this course must be expected to be milder than the natural history of AAA, since preventive actions are taken as consequence of the diagnosis and surveillance [see later].

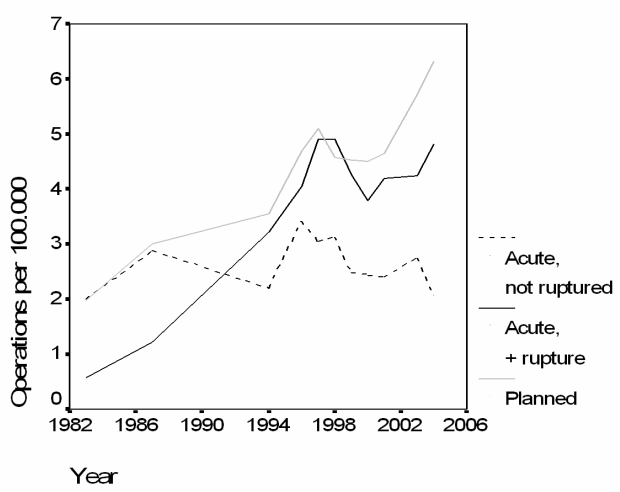
The AAA may be stable without further progression or progress and lead to rupture, if death has not occurred of other reasons. The most powerful predictor [Def.: Risk factors that are used to predict future events[27]] of rupture so far detected is the AAA diameter. This risk factor predicts a rapidly increasing risk when the AAA diameter grows to more than 50 mm. In asymptomatic AAAs with a diameter below 50 mm, the incidence of rupture was 0-0.5% annually, unless the AAA expanded rapidly [more than 6 mm per 6 months][72;73;73-75].

Autopsy studies have shown that 50% of AAAs with a diameter above 50 mm had ruptured[45;72;75;76]. Their mean risk of rupture is estimated at 5-6% annually[72-80].

The largest cohort of patients with large AAA [>50 mm] followed, were group of 476 canadian patients unfit for surgery with CT scans every 6 months until rupture, surgery, death, or deletion from follow-up. The average risk of rupture in male patients with 50-59-mm AAA was 1.0% [SD: 0.01%] per year, and in female patients 3.9% [SD: 0.15%] annually. The annual rupture rate in male patients with 60 mm or greater AAA was 14.1% [SD: 0.18%] per year, and 22.3% [SD:0.95%] in woman[81].

The second largest prospective cohort of patients with large AAAs unfit for surgery originates from the ADAM study, and included 198 patients [199]. The 1-year incidence of rupture was 9.4% for AAAs of 55 to 59 mm, 10.2% for AAAs of 60 to 69 mm [19.1% for the subgroup of 65-69 mm] and 32.5% for AAAs of 70 mm or more. Among AAAs reaching 80 mm, 26% ruptured within 6 months[82]. A summary of studies analysing the predictive capacity of the size of the AAA to predict rupture is collected in table 3. Large variations exists – probably partly due to different clinical consequences of an AAA at various stages. In general, the annual rupture risk af AAA below 55 mm seems to be 1% or less.

Figure 3. The incidence of operations for AAA from 1983 to 2004 in Denmark, stratified by indication of surgery.



Author	Year	N	Sex	Maximal AAA diameter (mm)							
				30-39	40-44	45-49	50-54	55-59	60-64	65-69	70+
Glimaker (73)	1991	187	M+F	0.4			9.3				
Sterpetti (75)	1991	297	M+F				2.6				7.4
Reed(83)	1997	181	M+F	0.0	1.0		11.0		26.0		
UKSAT (69)	1998	1090	M+F		1.0			6.5			
Scott (84)	1998	218	M+F	0.7		1.7					
Lederle (82)	2002	198	M+F					9.4	10.2 (19.1*)		32.5
Brown(81)	2003	377	M				1.0		14.4		
Brown (81)	2003	99	K				3.9		22.3		
Brown (85)	2003	688	M	0.0							
Brown (85)	2003	207	K	0.0							
EVAR-II (86)	2005	172	M+F					9.0			

Table 3. Studies concerning the association between the size and annual rupture risk of AAA

Furthermore, the risk of rupture grows with an increasing ratio between the AAA diameter and the suprarenal aortic diameter or the diameter of the third lumbar vertebra, fusiform AAA, AAA-diameter/length ratio, AAA blisters and high expansion rate. Smoking, diastolic hypertension, absence of lower limb arteriosclerosis and COPD are also associated with increased risk of rupture[51;73;75;78-80;87-91]. Seasonal variation have also been described with the highest incidence in autumn and late spring[92-95], while others could not detect this association[87]

In addition, the UK small aneurysm trial followed 2,257 AAA patients and found that the risk of rupture was independently and significantly associated with female sex [$p < 0.001$], large initial aneurysm diameter [$p < 0.001$], low forced experiatory volume during the first second [FEV1] [$p = 0.004$], current smoking [$p = 0.01$] and high mean blood pressure [$p = 0.01$]. Age, body mass index [BMI], serum cholesterol concentration, and ankle/brachial pressure index [ABI] were not associated with an increased risk of aneurysm rupture[96].

1.5. ARE THE INDICATIONS FOR TREATMENT CLEAR?

1.5.1. Asymptomatic cases

As mentioned, the risk of rupture increases rapidly when the AAA reaches 5 cm in maximal diameter. However, some AAAs below 5 cm in size rupture, while some above 5 cm never rupture. When our screening trial started in 1994, the size criteria were in most centres 5 cm varying from 4 to 6 cm in size[63;97-103]. However, at that time "The UK Small Aneurysm Trial" in the UK[69] and the similar ADAM study in the USA[68] both randomised approximately 1000 4.0-5.5 cm AAAs to operation or watchful waiting. After five years, no differences were noticed with respect to AAA-specific mortality. Consequently, a size criterion of 5.5 cm is now used by most surgeons. In addition, since AAA with rapid expansion have been associated with increased risk of rupture, many use an expansion of more than 6 mm per 6 months, as an indication for surgery[72;73;73-75]. However, in the end, the decision to operate asymptomatic cases is taken with due regard to age, the size of the AAA, the risk of the operation due to coexisting diseases and the patient's opinion, but clear indications for treatment seem present.

1.5.2. Symptomatic cases

A ruptured AAA requires immediate surgery as the patient will otherwise die. However, potential candidates for surgery are selected preoperatively. Some surgeons believe that they can predict fatal cases, but no valid evidence-based, sufficiently predictive tools are available, and even patients with the poorest prognosis sometimes survive surgery[104-106].

An increasing amount of evidence suggests that the results of operation for ruptured AAAs could be improved. Firstly, a critical role of postoperative intra-abdominal hypertension called abdominal compartment has been revealed. Such hypertension produces intestinal ischemia with translocation of endotoxins, renal failure, cardiac failure and respiratory

failure. This cause of multiorgan failure [MOF] seems preventable and initially reversible by leaving the abdominal incision open or inserting a mesh. In a case control study, patients who underwent mesh closure at the initial operation [n = 35], had significantly lower MOF scores, and they tended to have lower postoperative mortality within 30 days [51% versus 70%] and were less likely to die from MOF [11% versus 70%; P <0.05] compared with the patients who underwent mesh closure after a second operation in the postoperative period for abdominal compartment syndrome[107;108]. However, no randomised trial has been conducted exploring this situation. Secondly, recent results from an unrandomised study in Copenhagen showed a more intra- and perioperative aggressive transfusion strategy of plasma and platets resulted in fewer needing postoperative transfusions, and a higher 30-day survival proportion [66% vs.44%; p = 0.02][109].

Symptomatic AAAs without rupture were usually operated on as soon as possible because of the very high risk of early rupture, but symptoms may be misjudged, e.g. overlooking AMI, acute pancreatitis, pneumonia, etc., so the operative mortality is high, about 25%[67].
Finally, as mentioned Cambria et al[71] showed that operation within 4 hours was associated with increased risk of death compared with delayed procedures.

1.5.3. Contraindications to elective surgery

High-risk patients are those who have severe coronary or valvular heart disease, decompensated COPD, severe cerebrovascular disease, chronic renal failure, hepatic cirrhosis with portal hypertension, and chronic disorders of the blood associated with bleeding dysfunction. Furthermore, the postoperative mortality within 30 days are substantial in patients who have had an acute myocardial infarction [AMI] within the previous 3 months or who have had pararenal aneurysms[110;111].

Patients with unstable or severely symptomatic heart disease should undergo preoperative coronary angiography and ventriculography. Pharmacological provoked stress testing is recommended for patients with clinical markers of serious coronary artery disease and other medical or physical factors that prevent any type of standard exercise stress testing. The peroperative mortality of such high-risk groups varies from 5-48%[76;112-118].

So far, the EVAR 2 trial has demonstrated that with a suitable anatomy such patients can receive endovascular treatment with a mortality risk of 7%, but with no clear advantage compared with watchful waiting[86]. However, this seem partly caused by an "intelligent watchful waiting" in the no-intervention groups, since so many were treated in spite of the randomisation to no intervention.

1.5.4. Endovascular treatment of AAA

A minimally invasive endovascular treatment [EVAR] has recently been developed to exclude asymptomatic AAAs from the circulation. Under local or epidural anaesthesia, an endoprosthesis is introduced through the femoral artery, placed under guidance of angiography, and secured by stents [Figure 4][17;18;119]. Restrictions in the use of EVAR are caused by a too wide, too short or too angulated supra-aneurysmal infrarenal aorta, or too wide, too narrow or too angulated iliac arteries. Consequently, only 33-50% of all AAAs can be treated by unfenestrated EVAR.

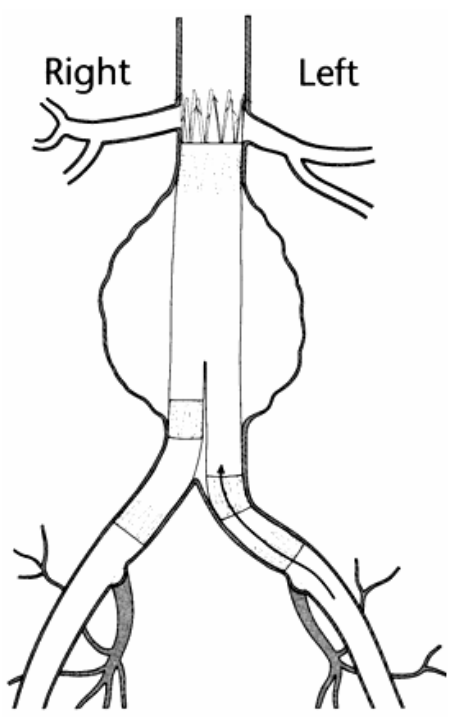


Figure 4. Endovascular treatment of an AAA. A Zenith graft with fixation proximally to the renal arteries. Implantation of the left prosthetic leg.

Compared with open surgery, the immediate results are good with similar or lower postoperative mortality within 30 days, fewer complications and shorter hospital stay without intensive care. However, disappointing long-term results have been reported which indicate a higher mortality due to a 1% annual rupture rate in treated cases and additional secondary interventions [2.1% annually], especially if conversion to open surgery becomes needed.[120-122]

Enthusiasts claim that the results are due to learning curves and that they stem from former generations of endoprostheses, while sceptics claim that the problems concerning unfixed anastomoses and latent endoleaks remain unsolved[123].

Randomised multicentre trials comparing open and endovascular treatment are now in progress, and results have been presented from the Dream trial[103;124] and the EVAR I and II trials[86;119;125;126].

In patients fit for open repair undergoing EVAR, the EVAR 1 trial [N=1082] reported a significant 30-day postoperative absolute mortality risk reduction of 3.0% in AAAs above 5.5 cm. In the smaller DREAM [N=351] trial of AAAs above 5 cm this figure was 3.4%. After four years, the overall mortality was similar in the two treatment groups, although the EVAR 1 trialists reported a persistent reduction in aneurysm-related deaths in the EVAR group [4% vs 7%; 0.55, 0.31-0.96, p=0.04]. They also reported that the proportion of patients with postoperative complications within 4 years of randomisation was 41% in the EVAR group and 9% in the open repair group [P<0.0001]. No difference in health-related QoL was noticed after 12 months, and the mean hospital costs per patient up to 4 years were £13,257 for the EVAR group versus £9,946 for the open repair group. Additional reinterventions and costs must be expected in the EVAR group. In all, EVAR seems to offer no advantage with respect to all-cause mortality and QoL, it is more expensive and it entails a greater number of complications and reinterventions. However, it did produce a 3% better aneurysm-related survival. The question is whether this is the proper end-point since it might be biased in favour of EVAR; the immediate deaths after open repair are very likely to be correctly classified, but death due to late rupture after EVAR risks misclassification. Furthermore, a relatively high proportion died before open repair due to a longer waiting time. Nevertheless, the EVAR 1 trialists emphasised the need for longer surveillance for a more detailed cost-effectiveness assessment.

The EVAR II trial[86] randomised patients with AAAs above 5.5 cm unfit for open repair to EVAR or surveillance. EVAR had a 30-day operative mortality of 7%, did not improve overall survival or AAA-related mortality and was associated with a costly need for continued surveillance and reintervention. However, a substantial part of those randomised to surveillance had surgery later.

The EVAR 1 and the DREAM trial results made a recent health technology assessment [HTA] conclude that the introduction of EVAR was a cost-ineffective failure[127], and another HTA calculated the incremental costs per saved quality-adjusted saved living year [QALY] to be approx. 650,000-1.3 mill DKK[128].

Selective cases of ruptured AAA have successfully been treated with EVAR, and it was for a while thought to be an attractive alternative for such critical ill patients in stead of open repair[129-131]. However, the frequency of ruptured cases suitable for EVAR has shown to be limited[132], and so far preliminary data from a randomised trial seem not to offer any benefit at all[133].

1.6. RECONSIDERATION OF THE EXISTING STRATEGIES FOR SOLVING THE HEALTH PROBLEM

In spite of a sufficiently known course of the disease without treatment and clear treatment probabilities, AAA seems to be an increasing major health problem in older men. Consequently, the Council of Europe recommends that the sufficiency of existing non-screening strategies is reconsidered in terms of possibilities of improving existing primary prevention and treatment opportunities, before screening is considered[25].

1.6.1. Possiblities of primary prevention

Risk factors for AAA seem similar to general risk factors for cardiovascular diseases. Risk facors are, however not, certain causes of AAA but characteristics that are associated with an increased risk of developing an AAA[27]. The distinction between association and cause is complicated. Sir Austin Bradford Hill recommended that such distinction must be based upon temporality, relative strong associations, dose-response relationship, reversibility, consistency, biological plausibility and analogy[134]. This seems to be a discussion out of the topic of this thesis, but shortly, apart from consistency, all these criteria can be questioned. More seriously, there seems no data available of whether such modifications can prevent mortality from AAA. Neither the cost utilities of such actions are available.

1.6.2. Reconsideration of the existing treatment startegies

Together with the increasing mortality, the tendency of an increasing incidence of emergency procedures together with an increasing number of planned operations, indicates that the additional elective operations performed, are not able to prevent the number of ruptured AAA to rise. This could be explained by insufficient numbers of elective operations relative to the total number of AAAs at risk of rupturing in the population, and/or an increased incidence of diagnosed symptomatic AAAs. The combination of increasing mortality and numbers of elective and emergency operations suggests a rising incidence and/or that AAAs are undergoing a more lethal natural history. Similar trends have been noticed abroad[45-49;52-63], but most are of older date, except in Western Australia where data are post-1992[56]. However, recently, an analysis from Malmö in Sweden between 1971 to 1986 and 2000 to 2004 showed the incidence of rAAA had increased significantly, despite a 100% increase in elective repairs[135]. Similar have been noticed in Wales[136].

1.7. CONSIDERATIONS OF A SCREENING PROGRAMME

1.7.1. The screening method

1.7.1.1. A suitable screening method

Screening for AAA with ultrasonographic scanning [US] is non-invasive and without any recognised risks. It only takes 5-10 minutes per scan by a trained nurse[16;63;137-139], and portable equipment is available for relatively low costs. Consequently, a suitable screening method seems avalialble.

1.7.1.2. A valid screening method.

Validation studies of US measurement of the aorta diameter describe an intraobserver SD of 1.3 mm, but the interobserver variation reportedly reaches 5 mm[32-34;140-145].

The interobserver SD of US scanning versus CT scanning is reported to be approximately 1.8 mm[140-143;146] with significant higher diameters measured by CT scanning; CT scanning is not capable of measuring the maximal diameter at a right angle, and it overestimates the measurements because the aorta follows the lumbar lordosis and the tortuous nature of an AAA. No golden standard for validating US as a screening method was therefore available until the introduction of 3D-image reconstructions. However, these techniques have not yet been used for validation, so the exact sensitivity and specificity is unknown.

1.7.1.3. An acceptable screening method?

In Northern Europe, attendance proportions to screening between 53-79% but mostly above 70% have been achieved[15;97;139;147-152], and attendance proportions at control scans have reached 94%[97;153]. These observations indicate an overall acceptable screening method.

However, the Council of Europe opinioned in 1987 that "the screening test must be acceptable to the population to be screened"[25]. There are three components in that issue: the intrinsic characteristics of the test, its sociocultural acceptability and the acceptability of the organisational arrangements for its provision. This means not only a sufficient overall attendance proportion, but sufficient attendance proportions for high risk groups.

However, this seems not even sufficiently to conclude screening for AAA is acceptable in high risk groups because sufficient attendance is not enough if the treatment is unacceptable for high-risk patients due to contraindications for surgery. This could leave a large proportion of untreated men at high risk of aneurysm rupture and those offered operation could have increased risk of postoperative complications and deaths. In all, the benefit of screening of a high risk group could be limited or in the worst case scenario even harmfull. On the other hand, the association between AAA and these diseases makes it possible that AAA screening could be restricted to such men.

1.7.2. Ethical, psychological and stigmatising consequences

Experience from non-AAA screening programmes point to risks of stigmatisation, fear, aggression, emotional reactions, psychosomatic reactions, social isolation, nocebo effects and "Blame the Victim" reactions[154-163]. QoL among attenders is reported to be lower before than after screening, which suggests some transient psychological stress, but changes are judged to be minor [164;165].

Screened subjects reported higher QoL scores after screening than controls, which may suggest that they saw their normal scan as a "certificate of health"[164-166]. This may inhibit their motivation for healthy life-style changes such as smoking cessation.

The QoL among non-attenders are reported to equal that of the non-invited controls[164;167].

The QoL in men having an AAA detected by screening is reported to be lower than among men with negative findings[164;166;168]. However, prospective data from the MASS trial suggest that this could be a pre-existing impairment that was more due to the higher proportion of co-morbidity than to the screening itself[169].

The Viborg Study and the UK Small Aneurysm Trial have reported that the conservative treatment of AAAs impairs generic and health-related QoL progressively, [164;170], but that QoL normalises after surgery[164;171-173]. In the most robust study, MASS trial could not either find any differences in the postoperative QoL in screen detected cases compared to controls[15]. Patients with randomly diagnosed AAAs also have a QoL that is similar to that of the sex- and age-matched population after both elective and emergency surgery[164;171;174-179], but posttraumatic stress and depressive symptoms have been observed[180]. Overall, there is no consensus about loss of QoL due to screening.

1.7.3. Potential target groups for screening

Research into the costs and benefits of screening for AAA should initially be conducted in the populations that would apparently enjoy the largest benefit. Since 60% of AAA-related deaths in Denmark occur in men and 86% of the deaths from AAAs in males occur at the age of 65 years or older, this group seems to be the optimal target group[62;63]. Earlier screening will probably require re-screening, consequently increasing the psychological and economic costs. However, theoretical calculations suggest that screening 60-year-old men may be just as cost-effective as starting at the age of 65[181]. However, this hypothesis has never been tested in clinical trials. If screening was offered later, more deaths from AAAs would occur, and the attendance proportion of those invited to screening must be expected to decrease. As an alternative, it may be relevant to screen men with increased risk of having an AAA, e.g. smokers, male siblings of AAA patients, men with hypertension, atherosclerotic diseases and COPD, but this has never been examined in clinical trials.

1.7.4 Acceptable treatments of the diagnosed disease?

At present, the treatment options are observation ["watchful waiting"] or operation.

Operations for AAA has an inborn mortality risk, so they may well cause more harm than good. However, if they are performed with the present accepted indications, they seem to lower the overall AAA-

specific mortality. We observed a statistically significant decline of 32% in AAA-related deaths immediately after the introduction of vascular surgery in Viborg County, Denmark, in combination with 33% more elective operations. This should be compared with an increase in AAA related deaths of 8% on a national basis[1].

The mortality risk of elective surgery was 3.8% in Denmark in 2005 [www.karbase.dk]. However, this risk may soon be reduced because beta-blockage has recently shown to reduce the mortality risk; patients with positive dobutamine-stress echocardiography were randomised to receive beta-blockage or standard care. The frequency of fatal AMI in the two groups was 3.4% and 17%, respectively. The frequency of all postoperative AMI in the two groups was 3.4% versus 34%, respectively[182].

In addition, in a retrospective study of preoperative treatment with statins and beta-blockers, the incidence of AMI or death within 30 days postoperatively was significantly lower among statin user than among non- users [3.7% vs. 11.0%; OR: 0.31 [0.13-0.74]; p=0.01]. Beta-blocker use alone was also associated with a significant reduction in the incidence of AMI or death within 30 days postoperatively [OR: 0.24 [0.11-0.54, P<0.01]][183].

Survivors after elective and after emergency surgery enjoy the same QoL as the population of the same age [164;171;174-179]. In some studies they even enjoy a better QoL[164;172;184-186], but survival tends to be shorter in general, significantly so in Canada, Norway, Sweden, and Minnesota[187-191]. However, these reports are based upon survival of patients with randomly detected AAAs. Since AAAs are normally asymptomatic, disease of some kind must have triggered the patient to contact the diagnosing doctor. This is not the situation in screen-detected cases. So, the long-term survival among screening-detected operated cases remains unknown.

The consequences of surveillance of AAA are mentioned above. Unfortunately, there seems to be no large materials available, specifying how many patients refuse operation or have one or more contraindications against operation. A personal communication between the randomised screening trials UK [MASS], Western Australia and Viborg was performed[102;147;192;193] which revealed that 336 out of 405 patients [83% [95% C.I.: 79-86%]] who meet the local size criteria for surgery were treated. As mentioned, the postoperative mortality within 30 days of a planned operation is reported to be 3-7%, which must be considered to be substantial in a preventive procedure. However, the risk must be balanced against the rupture risk of not being operated, which seems to be at least twice as high annually [Table 3]. Consequently, the risk reduction by elective surgery in cases above 5.5 cm is substantial, and illustrates a true ethical dilemma which is insoluble at the moment; some dying of planned surgery would never have felt any life threatening symptoms from their AAAs.

The outcome of surgery must also be acceptable in terms of morbidity and complications, and surgery is encumbered with a substantial risk of complications.

The permanent Gloucester screening program have reported lower mortality from operations of screen-detected than from non-screen-detected AAAs[194]. However, this may be due to selection, and perhaps also to earlier surgery in screen-detected cases which will produce a group of more fit patients. Further analyses on intention to treat basis from randomised screening trials would be helpful to answer this question.

1.7.5. Optimal interval screening and surveillance

The Council of Europe also demands the intervals between screening procedures to be clearly specified. It has been claimed that one single scan at the age of 65 is enough. However, the prevalence of AAA increases with age, and people live longer, also after development of other cardiovascular diseases. If screening programmes start at the age of 65, the men will at present live on average another 10-15 years. This seems sufficient to develop a clinically important AAA. However, there were no data available when we started the trial.

1.7.6. Benefits and cost effectiveness of screening

The benefits and costs of a screening programme are important and central criteria to be judged, and one of the major reasons for the Danish authorities to expand the criteria formulated by the Council of Europe. Several theoretical cost-benefit analyses had been performed in the last 20 years. Bengtsson et al. calculated that the Swedish AAA mortality would be reduced by 75% to the costs of SEK45,500 per saved life[195]. In the UK, Collin[196] and Heather[152] found the costs per saved life to be £9,000 and £4,000, respectively, while Mason found no benefit[197]. In the USA, Ernest[198] found reduced mortality and costs of AAA treatment, while Frame[199] calculated the costs to be US$28,741 per saved living year and Quill[196;200] US$ 212,000 per saved life because of high expenes for the scans and operations in the USA.

In Denmark, we calculated that screening 100,000 65-year-old males would avoid 672 AAA-related deaths before the age of 80, but they would partly be replaced by other deaths, so the net benefit would be 445 avoided deaths, corresponding to 3,400 saved years of life at a cost of DKK10,000 per saved living year[201].

Similarly, a recent Swedish analysis calculated the costs to be SEK7,760 per saved living year and SEK9,700 for a quality-adjusted life-year[202]. A similar conclusion was reached by a Finnish group[203]. In agreement with this study, a recent Dutch analysis by Boll et al. calculated the cost per saved living year to be €1,176[204].

Another Swedish theoretical analysis by Wanhainen[181] analysed different screening strategies in terms of age [60, 65 or 70 years] and risk

profiles [all men or specific high-risk groups] of the screened population, and rescreening after 5 or 10 years by a Markov simulation cohort model. The cost per life year saved ranged from US$8,309 to US$14,084 and was estimated to US$10,474 dollars when 65-year-old men were screened once. Interestingly, screening 60-year-old men was calculated to be just as cost-effective as offering screening to 65-year-old men, and a trade-off between high prevalence of AAA and lower life expectancy eliminated the expected benefits of screening high-risk groups such as smokers - a result in contrast to the recommendation by the American Preventive Task Force [se later].

Nevertheless, the majority of the analyses point in the same direction, but are probably also made by enthusiasts of screening which could influence the assumptions needed to be taken for the analyses, which would require that interpretation of these results should be cautious[205].

However, such models always rely on some uncertain assumptions. The only valid data are those obtained from randomised screening trials with cost estimations. However, only one study seemed to exist when we started our screening trial, but they did not include any cost estimations.

1.7.6.1. Potential additional benefits of screening for AAA. Prevention of cardiovascular morbidity and mortality

As mentioned, operation for AAA is encumbered by a substantial risk of complications and death, and carries the far most economic burden by offering screening. However, the majority of AAA diagnosed by screening is too small initially to be recommended for operation. The early detection allows general cardiovascular prevention to be taken. Patients with randomly diagnosed AAA are known to have higher mortality than age-matched controls, especially due to cardiovascular diseases. Since AAA is associated with COPD and cardiovascular disease[43;139;206-218], ongoing screening could provide an opportunity to prevent morbidity and mortality from other causes through appropriately targeted intervention. However, an important remaining question is whether men with AAA without manifest cardiovascular disease or COPD have a higher mortality due to these disorders and may therefore benefit from preventive actions.

PART II. PREDICTION OF THE CLINICAL COURSE OF AAA

Most AAAs diagnosed by screening are too small initially to be recommended for operation, but a considerable proportion expand further and require later surgery. This growth phase makes the AAAs a unique object to study risk factors for their progression.

There are several good reasons to search for predictors of the clinical course of AAA. Even identification of predictive markers [Def.: a risk factor that is not a cause of the disease[27]] could be of major value. Small AAAs do occasionally rupture and AAA surveillance has psychological side-effects and involves impaired QoL. Earlier AAA surgery may produce more safe surgery and better QoL. Identification of predictors of expansion and future need for surgery would be able to provide us with a more nuanced indication for operation. On the other hand, only about half of those operated would have experienced rupture if the AAA was left unoperated. However, such markers of aneurismal progression are also surrogate markers of rupture, and they may provide us with more selective tools for the management of larger AAA. They may also be useful in present resource-demanding surveillance of EVAR-treated patients. Finally, they can provide us with new knowledge of the pathophysiology of AAA, causes of AAA and thus be targets for potential prevention or pharmacological inhibition.

2.1. PHYSICALLY RELATED PREDICTORS

One of the first and still most powerful predictor of aneurismal growth and rupture is the size of the AAA suggesting an important physical role. Since the late eighties, the predictive value of the physical properties of AAA has been investigated.

2.1.1. Elasticity or compliance of the AAA wall

Ultrasongraphic based wall stress analysis was used initially[219-221]. We have earlier reported that the level of various proteases involved in the aortic matrix degradation correlates with aortic compliance and elasticity[222]. In spite of a relatively high variation of measurements, such ultrasonographic analysis has shown a potential to predict later rupture[220;223], but it has never gained much attention - probably due to the difficulty of performing measurements. A recent long term follow up of the measurements we made of the cohorte of small AAA in 1998[222] showed a poor to modest correlation with the annual expansion rate [Not yet published].

2.1.2. Infinite element analysis

Recently, AAA wall stress distribution has been computationally determined in vivo with CT data, three-dimensional computer modelling, finite element analysis [nonlinear hyperelastic model depicting aneurysm wall behaviour] and blood pressure during observation. This model has also shown potential to predict rupture[224-228], but robust clinical studies are still missing.

2.1.3. Calcification of the AAA wall

In spite of its obvious potential importance for the strength of the AAA wall, only few have investigated the role of calcification of the AAA wall, and mostly in connection with the diagnosis of ruptured AAA, complications efter endovascular procedures, and the regression of the aneurysmal sac after exclusion by EVAR. However, one retrospective study demonstrated

an association with hypertension, coronary artery disease, and peripheral vascular occlusive disease in 129 cases with AAA wall calcification above 40% of the circumference judged by CT scanning [229]. Another study found no relation to rupture[230]. Apparently, no studies seem available concerning small-middle sized AAA.

2.2. BIOLOGICAL PREDICTORS

2.2.0. Definitions

A predictor is a risk factor that is used to predict future events. A risk factor is a characteristic that is associated with an increased risk of an event. Risk factors may or may not be a cause of the event. A marker is a risk factor that is not the cause of the event[27].

2.2.1 Markers of aortic matrix metabolism - elastin and collagen

Elastin and collagen are the major matrix components of the human abdominal aorta. In AAA, the structure and the amount of both these matrix proteins are changed[231]. The amount of elastin decreases while the amount of collagen increases[231-235]. Increased levels of elastase in aneurysmal walls[231;236;237] and increased systemic levels of PIIINP created by neocollagenesis have been reported in aneurysmal cases[238].

We have earlier reported elastin peptides [EP] levels to be one of the strongest independent predictors of the expansion of small AAAs[239] and in a multivariate model including initial AAA size, EP and NPIIIP we predicted that together these parameters would predict cases reaching 5 cm in diameter within five years with a sensitivity of 91% and a specificity 87%[240]. Furthermore, in collaboration with the Chichester Aneurysm Screening Study we later reported that EP levels were more predictive for cases becoming symptomatic or rupturing than the last measured AAA size[241]. Unfortunately, the ELISA is polyclonal and different generations of ELISA show poor correlation, so a standardised ELISA needs to be developed before clinical application is possible[242]. Alternatively, Desmorine - the specific common final degradation product of elastin – could be used. However, it has never been examined[243-245].

2.2.2. Involved proteases in the pathogenesis

At least three proteolytic systems seem to be involved in the degradation of the aorta that may lead to AAA and its further progression.

2.2.2.1. Serine-dependent proteases

The levels of elastase have been found to be significantly raised in aneurysmal walls compared with aortic walls of occlusive atherosclerosis. They were increased fourfold in ruptured cases compared with occlusive aortic atherosclerosis[231;236;237;246-248].

Elastase in blood is immediately inactivated by antiproteinases, mainly alpha-1-antitrypsin. Recently, we reported that the expansion rate of small AAAs correlates with the level of elastase-alpha-1-antitrypsin complexes[249].

2.2.2.2 Metallodependent matrix proteases

Levels of various metallo-dependent matrix proteases, especially MMP2 and MMP9, have been found to be elevated in aneurysmal aortic walls compared with aortic walls of occlusive atherosclerosis. Increased MMP2 levels have been detected, in particular, in small AAAs, while MMP9 levels seem especially increased in large AAAs. They are mainly inhibited by TIMP-1 and TIMP-2[250-256].

In a small study [N=32], we showed that the plasma level of MMP9 correlated with the expansion of small AAAs [r=0.33 [0.01-0.53]], while MMP2, TIMP1, and TIMP2 did not. However, a larger sample size is needed for evaluation of the clinical value of this observation[257].

Recently at Leiden University, increased type I collagen degradation products was found in asymptomatic and ruptured AAA compared to controls, and mRNA and protein analysis identified neutrophil collagenase [MMP8] as the principle collagenase together with cysteine proteases [see 2.2.2.3 below] by an 3 fold increase[258].

The strong association have simulated search for genetic dispositions for AAA in various MMP and TIMP polymorphisms. Jones et al.[259] reported C-1562T polymorphism of MMP9 – a potential central protease in the AAA pathogenesis, but others did not find any association[260-263]. Ogata et al. found MMP10 polymorphism to be associated with AAA[262].

Eriksson et al. also investigated the relationships of MMP-12 in addition to MMP-2, -3, and -9, and found no evidence that any specific MMP polymorphism had a clinically significant effect on aneurysm expansion[264].

Ogata et al. also found an association between AAA and the TIMP-1 and 3 polymorphisms in male patients without a family history of aneurysm[262] and Wang et al. found TIMP-2 polymorphism associated with AAA[265].

In all, no certain and consistent association seems to has been revealed.

2.2.2.3. Cysteine-dependent proteases

Three elastolytic cysteine proteases, cathepsin S, L & K, were recently isolated, and an over-expression in atherosclerotic lesions compared with normal arteries was demonstrated[266;267]. In vitro studies have shown that alveolar macrophages from cigarette smokers, or monocytes stimulated by gamma-interferon, secrete less cystatin C [the quantitatively dominant inhibitor of catepsins] than unstimulated macrophages or monocytes. This would seem to suggest the possibility of reduced cystatin C in inflammatory areas [268]. Finally, circulating levels of cystatin C have been reported to

be decreased in aneurysmal cases compared with a sex- and age-matched control group[269].

At Leiden University, a fivefold increase in cathepsins K and L, and a 30-fold increase in cathepsin S activation were found together with a 3 fold increase in MMP8 in asymptomatic and ruptured AAAs, respectively. Protease inhibitor mRNA expression was similar in AAAs and controls, but AAA protein levels of cystatin C were profoundly reduced [>80%] suggesting degradation of the inhibitors in AAA [270].

We have previously found that S-cystatin C correlated negatively with AAA size [r= -0.22 [-0.59; -0.02]] and annual expansion rate [r= -0.24 [-0.75; -0.05]]; a correlation that persisted after adjustment for renal function, smoking, diastolic blood pressure, CRP, age and AAA. The level of s-cystatin C was significantly predictive of cases becoming recommendable for surgery with an optimal sensitivity of 61% and a specificity of 57%; levels that are hardly sufficient alone for clinical use[271].

2.2.3. Activation of the involved proteases

2.2.3.1. Plasmin

Apart from its fibrinolytic function in plasma, plasmin also plays a central role in the activation of the degenerative processes in tissues. Thus, plasmin is a common activator of the three above-mentioned proteolytic systems[272;273] and it could thus be involved in AAA pathogenesis. Plasmin is immediately inactivated in the blood by antiplasmin forming plasmin-antiplasmin [PAP] complexes[274].

We have previously reported that the level of PAP was positively correlated with the annual expansion rate [r= 0.39, p=0.01] and that it persisted after adjustment for initial AAA size, EP and smoking. Furthermore, the PAP levels were significantly predictive for cases expanding to operation-recommendable AAA sizes with an optimal sensitivity of 65% and a specificity of 67%. Combined with the initial AAA size, the optimal sensitivity and specificity were both 82%[275].

The plasmin pathway may be central in the pathogenesis.

2.2.3.2. Plasminogen activation

Plasmin is activated by an urokinase-like plasminogen activator [uPA] and tissue-like plasminogen activator [tPA], which is mainly inhibited by plasminogen activator inhibitor 1 [PAI-1] among others. There is a polymorphism of the PAI-1 gene in position -675, which has been associated with relatively reduced transcription of PAI-1[276], and reported to be more frequently present in AAA-patients[276], and the progression rate of AAA[277]. It seems of major importance to clarify the activating pathway of this apparently key protease in the progression of AAA, and triggering factors of this pathway.

2.2.4. An autoimmune or infectious disease caused by C. pneumoniae?

Seroepidemiological studies have shown an association between C. pneumoniae and atherosclerosis and the risk of AMI[278-284]. Furthermore, several studies have detected C. pneumoniae DNA and antigen in atherosclerotic lesions from coronary and carotid arteries, and in AAAs[280;285], but the validity of the methods deployed are debatable [280;286-288] and the association between the direct and indirect methods of detection is poor[289]. In addition, all randomised trials concerning macrolide treatment have been disappointing, except two small initial ones which demonstrated a transient if any benefit at all[290-292]. The poor results may be due to insufficiently eradication of C. pneumoniae organisms or no influencing organisms to eradicate, and the transient benefit could be a random finding or caused by the well-known non-specific anti-inflammatory effect of macrolides[293].

At the moment, the role of C. pneumoniae in atherosclerotic and aneurysmal disease remains unknown, and the clinical impact of detecting the organism is unresolved. The lack of benefit of antibiotics and questionable detection methods point to the direction that C. pneumoniae are not present in the lesions, and thus do not participate directly in the progression of atherosclerotic and aneurismal progression. However, in the screening-diagnosed AAA cases, we found a very high prevalence of seropositivity of C. pneumoniae up to 83% depending on the definition. The upper 99% confidence limit was close to 100% concerning an IgA-titre of 20 or more, or an IgG-titre of 32 or more[294].

We have previously reported that IgA > 20 was associated with a 50% increased expansion rate and that it remained an independent predictor of expansion by a relevant multivariate analysis[294]. These results were confirmed in a cohort of aneurysmal cases from the Chichester Aneurysm Screening Study[295]. In addition, during validation of a new ELISA, we observed that by ROC curve analysis the titres were predictive for cases of AAA that would expand to sizes at which surgery would be recommendable within five years[296]. The discrepancy between a questionable presence in cardiovascular lesions, the lack of benefit from antibiotic treatment and strong seroepidemiological evidence of a connection could be explained by an autoimmune reaction called "molecular mimicry"[297]. In childhood and adolescence, upper respiratory tract infections with C. pneumoniae are common, so the immune response is triggered to fight the C. pneumoniae antigens. The damaging of the vascular wall, whichever the reasons, may lead to presence of antigens that look like the C. pneumoniae. The present major question of interest is – are Chlamydia pneumoniae really present in AAAs, and if not, what are the C. pneumoniae antibodies in the patients then reacting against?

PART III. CONDENSATION OF BACKGROUND AND AIMS

AAA seems to be an increasing, major health problem in older men and for the society, and the existing preventive and treatment strategies seem to have failed to stop that development. Ultrasonographic scanning seems to be a suitable and acceptable method of screening but the exact sensitivity and specificity of such screening remain unknown. An acceptable treatment of asymptomatic cases is present. So screening for AAA may be an alternative to the present strategy. However, the feasibility, attendance proportion to screening of invited men, prevalence and incidence of asymptomatic AAA, the incidence of ruptured AAA and AAA-related mortality in older Danish men, and whether such mass screening for AAA reduces AAA related mortality after five years is unknown. If screening programmes start at the age of 65, the men will at present live on average another 10-15 years. This seems sufficient to develop a clinically important AAA, but the need for re-screening is unknown. Consequently, Study I was designed to determine the feasibility of a Danish hospital based screening programme of 64-73 year old men, their attendance proportion to screening, the prevalence and incidence of asymptomatic AAA, and the potential need for interval screening including analyses of selective possiblities. The incidence of ruptured AAA and AAA-related mortality in Danish men aged 64-73, and in particular to analyse whether hospital-based mass screening for AAA reduces AAA related mortality after five years.

Patients with incidently detected AAA have been associated to cardiovascular diseases, but the association is poorly described in population based mass screening. If the association also is present in patients with screen-detected AAA, it might be possible, that AAA screening could be restricted to such men, but on the other hand, the benefit of such screening of a high risk group could be limited or in the worst case scenario even harmfull. Consequently, Study II was designed to perform a stratified analysis in the above mentioned randomised population screening trial for AAA in men, with or without hospital diagnoses of chronic obstructive pulmonary disease [COPD] or cardiovascular disease, in order to evaluate whether the offer of screening is acceptable to those at high risk of having an AAA, and to evaluate whether the offer of screening may be restricted to such men in high risk.

The benefits of screening accumulate with time; so long term results are of major interest, but unknown. In addition, estimation of the cost effectiveness of such a programme is essential for an overall evaluation of the WHO criteria. Consequently, Study III was designed to perform a long term analysis of whether hospital-based mass screening of Danish men aged 64-73 for AAA reduces AAA related mortality and overall mortality after fourteen years of follow up combined with a cost effectiveness analysis of the costs per gained living year performed by the state-of-the art. In addition, as a programme would be concerning men aged 65, a subgroups analysis of that age group was performed, as well as concerning those with and without diagnoses of chronic obstructive pulmonary disease [COPD] or cardiovascular disease because detection of AAA in those with associated comorbidity would require less screening costs to detect an AAA, but due to a higher operative risk, a higher proportion of those with operation demanding large AAA who are unfit for surgery will be higher, as well as the postoperative morbidity and mortality. Factors which affect the benefits and cost-effectiveness of such high risk screening.

Most AAAs diagnosed by screening are too small initially to be recommended for operation, but a considerable proportion expand further and require later surgery. This growth phase makes the AAAs a unique object for pathogenetic analysis of their progression and holds a key for potential medical intervention.

The influence of the physical properties on the progression of AAA have interested researchers the last two decades, but influence of the wall calcification judged by ultrasonography on aneurysmal growth rate and need for later surgery is unknown. Consequently, Study IV was designed to investigate whether the degree of AAA-wall calcification judged by ultrasonography is associated with the aneurysmal growth rate and whether calcification is associated with later surgery.

The matrix degradation causing the progression of AAA is caused by at least three proteolytic systems of which plasmin is a common activator of the three systems. Therefore, the potential pathways in the plasmin activation associated with the progression of AAA could be of major importance. Consequently, Study V was designed to study the potential pathways in the plasmin activation associated with the progression of AAA, and the potential roles of smoking, homocysteine, Serum IgA-antibodies against Chlamydia pneumoniae [IgA-CP], Macrophage inhibiting factor [MaIF], and Tumor growth factor beta-1 [TGF-Beta-1] in these pathways. In addition, to correlate aneurismal progression with smoking and hyperhomocysteine, as this could reveal potential inhibition of aneurismal progression through smoking cessation and vitamin supplies.

The role of C. pneumoniae in AAA remains unknown. The lack of benefit of antibiotics and questionable detection methods point to the direction that C. pneumoniae are not present in the lesions, and thus do not participate directly in the progression of atherosclerotic and aneurismal progression. However, the progression of AAA is associated with presence of antibodies against C. pneumoniae. An interesting question is still whether the bacteria is present in the AAA-wall, and if not what the antibodies are cross reacting against. Consequently, Study VI was designed to detect outer membrane protein [OMP] from Chlamydia pneumoniae in AAA wall tissue by use of antibodies against OMP from Chlamydia pneumoniae

purified from AAA patients and to search for potential cross-reacting proteins in the wall of AAAs.

As mentioned, early detection of AAA holds a key for medical intervention. Screen-detected AAA may be associated to cardiovascular diseases. Consequently, Study VII was designed to analyse whether men with AAA not previously hospitalised with cardiovascular disease or COPD have higher mortality due to these disorders and therefore may benefit from preventive actions.

PART IV. METHODS AND MATERIAL

4.1. METHODS USED IN STUDY I.

4.1.1. Randomised mass screening of [64] 65-73-year-old men

During 1994 we randomised all men living in Viborg County and born in 1921-1929 using their civil personal registration [CPR] number. Randomisation was performed using the software in Epiinfo version 5 and took place in blocks of approx. 1,000 persons to avoid long delay between randomisation and invitation to screening. During 1995-1998 we randomised all of those who turned 65 years old that year[16;63].

The men were assigned randomly and individually in a ratio of 1:1 to receive a screening offer or to enter the control group. Randomisation produced 6,306 male controls, and 6,333 were invited to receive an abdominal ultrasonographic scan [US] at their regional hospital, where appointments were made at 5-minute intervals. Fasting was not required and support for transport to the hospital was not provided.

The invitation allowed the participant to change the time of the appointment or to refuse the invitation. Non-responders were reinvited once at an interval of 3 per 5 minutes. A doctor and a nurse who were specially trained in US techniques alternated in organising, examining and registering the scans. An AAA was defined as a maximal abdominal aortic diameter of 30 mm or more.

When our screening trial started in 1994, the size criteria were in most centres 50 mm. So AAAs of 50 mm or more were referred for CT-scanning and preoperative evaluation by a vascular surgeon. Due to later results from two large RCTs[69], a size criterion of 55 mm are now used by most surgeons. Men with an AAA of 3-4.9 cm were offered annual follow-up for aneurysmal expansion.

Survivors with an ectatic aorta [def.: infrarenal aortic diameter of 25-29 mm or distal/renal aortic diameter ratio>1.2] diagnosed in 1994-96 were invited for rescreening after 3-5 years[63;298;299].

4.1.2. Ultrasonography as screening method

B-mode scans were performed by one to three alternating observers with one mobile Phillips SDR 1550 [35 kilograms] and a 4-MHz linear transducer. A strict standardised method of observation was used. The aorta was identified by a longitudinal view, and it was visualised from as proximally as possible to below the bifurcation. The transducer was then transversed, and scanning was started as proximally as possible. The anterior-posterior [AP] and transverse diameters were measured at the level of the crossing left renal vein. If the vein was not visible, it was measured as proximally as possible. The distal aorta was then examined. When no dilatation was present, the aorta was measured just above the bifurcation. The scanning was not completed before the bifurcation was seen. When dilatations were noticed, the maximal AP and transverse diameters were measured. In case of a diameter of 30 mm or more, the right-angled maximal AP diameter by a longitudinal view was recorded and used as basis for AAA-surveillance [see below].

Blinded validation studies of the examinations showed a standard deviation [SD] of the intraobserver variability of measurements below 0.5 mm[32;63].

In 50 cases, weight, height and period from the last meal was recorded, and blinded measurements were carried out by two observers. The interobserver variability was judged by the Spearman's correlation coefficient, and calculated as twice the SD[32].

We found that the distal aortic measurement showed good reproducibility [r=0.98] and an interobserver variability of 1.46 mm. The mean difference was 0.1 mm [P=0.77]. No correlation was noticed between interobserver variability and the period from the last meal, or body mass index [BMI] with respect to the distal measurements [r=0.14 and 0.02, respectively]. The proximal infrarenal aortic measurement showed lesser reproducibility [r=0.77] and a variability of 2.90 mm. The observed mean difference of 0.88 mm was significantly different from zero [P=0.001][32]. There was a significant correlation between differences in the measurements between the two observers and both the period from the last meal and BMI [r=0.35 and 0.32 respectively] with respect to the proximal measurements[32].

Increased variability of the measurement of the proximal part has also been observed by others[32-34].

Our observed variability of the distal measurements were relatively small compared with others, who often find discrepancies of 5 mm or more[32-34;140-145].

Apart from questioning US as a reliable screening method, such large variability questions the method for surveillance of small AAAs, and emphasise the need for standardised observations with interval quality checks.

It seems likely, that the relatively small variability in the present study was obtained owing to our highly standardised method of measuring the AP diameter [See methods used in Study IV, below].

4.1.3. Identification and classification of deaths and operations

All Danes are registered at birth with a 10-digit personal identification number, the CPR number, which is used for unique identification of address, causes and dates of hospital admissions and deaths, etc. Data concerning all inhabitants can be traced and used in

epidemiological research, making selection bias minimal.

Deaths were identified in the Danish Civil Register. We initially randomised 12,658 men, but when data concerning deaths during the first five years after randomisation were obtained, it became clear that 19 of the randomised men were dead at the time of randomisation, but had not yet been deleted from the registry. They were excluded from the material which leaves a discrepancy between the reported numbers in the preliminary analysis from 2002 and the later reports[16;298]. In all, 12.639 men were included. Hereafter, deaths certificates with AAAs as the primary or a contributing cause of death were identified in the National Registry of Causes of Deaths. Hospital records and autopsy records were collected concerning cases caused by AAAs or with AAAs as a participating cause of death. Two vascular surgeons, who were blinded to the randomisation group and to each other's evaluations, assessed the information, and each assessed the deaths to be certainly, possibly or not caused by AAAs. Cases where both assessors evaluated the death to be certainly or possibly caused by AAAs were classified as AAA deaths.

No matter how careful the evaluation is, deaths due to AAA risk misclassification; a man with a known AAA who dies at home due to cardiac arrest risks the cause of the death to be classified as AAA rupture, while a man dying at home of a ruptured but unknown AAA risks classification of cardiac related death. Both types of information bias impair the apparent benefit of screening, especially due to the high prevalence of cardiovascular co-morbidities in AAA patients.

AAA operations were identified nation-wide in the Danish Register of Vascular Surgery ["Karbasen"], which has shown to be quite valid concerning registration and classification as planned or emergency operations with and without rupture, because the postoperative morbidity and mortality depends on this, and the frequencies were expected to be influenced by the offer of screening.

4.1.4. Statistical analyses

Analyses on an intention to screen basis from the date of randomisation to 31.12.1999 were performed. Fisher's exact test was used to compare proportions. Cox proportional hazards regression to compare specific mortality due to AAA and overall mortality. Separate analyses for the periods before and after 1.5 years after randomisation due to the proportional hazards assumption was not fulfilled.

The expected number of life years gained within 5, 10, and 15 years for two hypothetical cohorts representing screened participants and controls were calculated, each of 6333 men aged 67. In the cohort representing the controls, the number of remaining life years was estimated from the life table for Danish men in 1995 and 1996. In the cohort representing the screened participants, the mortality for the period 1.5 to five years after randomisation was assumed to be reduced as observed.

4.1.5. Discussion of analyses of benefit – length bias and lead time bias

The evaluation of a screening programme risks length bias which causes a too optimistic evaluation, if the duration of the disease varies as more benign cases will be overrepresented. Consequently, the seriosity of the disease and the benefit of screening cannot be evaluated upon the prevalence itself but needs to be evaluated due to causes of illness and/or death. As AAAs is mostly asymptomatic until rupture, the best evaluation variable would be deaths or survival. When analysing survival, one cannot use the survival after being diagnosed with an AAA, as screening obviously will cause AAA to be detected earlier compared to incidently diagnosed cases of AAA causing lead time bias. Consequently, the analyses were performed based upon the intention to treat principle from the data of randomsisation.

4.2. METHODS USED IN STUDY II

4.2.1. Randomised mass screening of [64] 65-73-year-old men

The study used the same methods as described in Study I [4.1.1.].

4.2.2. Ultrasonography

The study used the same methods as described in Study I [4.1.2.].

4.2.3. Identification and classification of deaths and operations

The study used the same methods as described in Study I [4.1.3.].

4.2.4. Morbidity classification

All previous discharge diagnoses recorded in the National Hospital Discharge Registry concerning chronic obstructive pulmonary disease [COPD] and cardiovascular diseases including hypertension were ascertained for all enrolled men up till the date of enrolment. This registry, established in 1977, records civil registration number, dates of discharge and up to 20 discharge diagnoses. Diagnoses were classified according to the Danish version of the International Classification of Diseases [ICD], 8th revision until the end of 1993, and the 10th revision hereafter[300]. Based on previous studies, the following groups among these codes were defined as AAA-associated diseases; hypertension, previous AMI, COPD, ischemic heart disease [IHD] excluding AMI, arteriosclerosis affecting the lower limbs [PAD], stroke or transient cerebral ischemic attack [TIA] [Table 4][II,VII].

All diagnoses were included, not only the primary diagnosis that caused the admission. The advantages of these computer-based data are the easy access and they are compiled on a national basis. They are

AAA-associated diseases	Included WHO classification codes	Included WHO classification diagnoses
Arteriel Hypertension (Hyp. Art.)	400.00-400.99 401.99 402-4.99 410.09 41.109 412-3.09 430.00-09 431.00+09 433-4.09 435.09 436.00-09 437.00-09 I10-I15	Hypertensio arterialis maligna Hypertensio arterialis essentialis benigna Mb. Cordis/Renalis hypertensivus Infarctus myocardii acutus cum hyp.art Mb. Cordis arterioscleroticus et subacutus alius cum hyp.art. Mb. Cordis Arterioscleroticus/Asymptomaticus cum hyp.art. Haemorrhagia subarachnidalis cum hyp.art. Haemorrhagia intracerebralis/cerebri cum hyp. art. Thrombosis/Embolia cerebri cum hyp. art. Ischaemia cerebri transitoria cum hyp. art. Mb. Cordis Cereborvascularis male definitus cum hyp. art Mb. Cerebrovascularis ischaemicus generalisatus cum hyp. art Hypertensio arterialis
AMI(1)	410.09+99 I21-I23	Infarctus myocardii acutus cum/sive hyp.art Infarctus myocardii acutus/Infarctus myocardii acutus recidivans
IHD excl. AMI (2)	411.09+99 413.09+99 I20	Mb. Cordis arterioscleroticus et subacutus alius cum/sive hyp.art. Angina Pectoris cum/sive Hyp.Art Angina Pectoris
COPD(3)	491.00-493.09 51.700-517.09 J40-J47	Broncitis Chronica, Emphysema pulm., Astma , Alia pneumonia chronica interstitialis Broncitis Chronica, Emphysema pulm., Astma , Mb. Chronicus Pulmonis Obstructivus Alius
PAD(4)	440.09+20,30,39 440.99 444.00,09,19 444.41-99 445.00-445.99 I70 (Excl.I70.1) I74 (Excl.I74.2)	Arteriosclerosis aortae/extremitatis inf./art.iliacae Arteriosclerosis universialis et non specificata Embolia/thrombosis bifurcationis aortae/aorta abdominalis Embolia/thrombosis Art. Femoralis/Art. Popliteae/Art. Tibialis/ Art. Periphericae Extremitatis/Art. Extremitatis alia definita/ Art. Extremitatis/ Art. Iliacae/ Art. Aliae non specificata Gangraena Arteriosclerosis Embolia et thrombosis arteriarum
Stroke or TIA (5)	431.00-432.99 433-4.09+99 435.09+99 436.01+90+99 I63-I64 I65-I66 I67	Haemorrhagia cerebri/Occlusio et stenosis Art. Precerebralis Thrombosis/Embolia Cerebri Ischaemia cerebri transitoria Apoplexia cerebri/Mb. Cerebrovascularis acutus male definitus Infarctus Cerebri/Apoplexia Cerebri non specificata Occlusio/Stenosis Art.Precerebralis/Art Cerebri sive infarctu cerebri Morbi cerebrovascularis alii

Table 4. The definitions of six high-risk groups for AAA based on classification of previous hospital submissions due to AAA-associated diseases according to the 8th and 10th WHO classification of diseases.

1: Acute myocardial infarction [AMI].
2: Ischemic heart disease [IHD]
3: Chronic obstructive pulmonary disease [COPD].
4: Peripheral occlusive arterial disease [PAD].
5: Transient ischemic attack [TIA].

also the likely selective tool if high risk screening is considered [II], since examining GP patient records is too time-consuming taking the time needed to perform an abdominal aortic screening scan into consideration. The disadvantages are the risks of misclassification and missing information about non-hospitalised patients, i.e. patients treated only by a GP.

For some diagnoses, e.g. hypertension [301], Danish studies have reported considerable misclassification bias with only 40-60% of cases being registered, although other cardiovascular discharge diagnoses such as AMI[302] and COPD have shown a positive predictive value both reaching 90%[303].

4.2.5. Statistical analyses

Differences in proportions were tested by Chi square tests. Hazards were used to estimate the AAA specific

mortality ratio by Cox regression analysis. The proportional hazards assumption was evaluated graphically. The survival analyses were calculated on the basis of intention to screen from the date of randomisation to death or 31.12.01.

4.3. METHODS USED IN STUDY III.

4.3.1. Randomised mass screening of [64] 65-73-year-old men

The study used the same methods as described in Study I [4.1.1.].

4.3.2. Ultrasonography

The study used the same methods as described in Study I [4.1.2.].

4.3.3. Identification and classification of deaths and operations

The study used the same methods as described in Study I [4.1.3.].

4.3.5. Estimation of costs

4.3.5.1. Screening costs

The cost of the screening was determined as the cost of a permanent screening programme with a maximum capacity of 6000 individuals being screened annually including a 25% load factor. The cost of the screening programme was assumed to be 169,000€ per year [see Table 5]. The equipment cost included the financial cost [interest 3% in real terms] and five years depreciation of the ultrasound and computer equipment [purchase price 35.000€ excluding VAT]. The average contribution to the fixed cost is assumed at 1.30€ per scanned person.

The organisation of a permanent screening programme was assumed to similar to the configuration in the trial and would require one nurse working four days a week [80% whole time equivalent] , one medical doctor working five days a week [one whole time equivalent, but supplemented with a secretary working one third whole time equivalent. It was assumed that staff could be recruited on ordinary conditions [average salaries]. Cost for recruitment and training of staff, and cost related to planning and management of the programme were assumed included in the load factor and 21% overhead costs.

The cost of sending out invitations to the target group was assumed to cost 3.20€ per invite and included time used by a secretary to retrieve addresses, write and pack letters as well as tracking non-participants. The cost also included costs related to office consumables including envelopes and stamps. The cost of conducting an ultrasound screening [excluding the use of ultrasound equipment and office rooms] was assumed to cost 23€ per scanned patient and include nurse and doctor time as well as contribution to their transport time and cost.

The derived cost of the screening programme included annual control screening of men with a 3-5 cm AAA, as well as the cost of a planned operative treatment, acute operative treatment with and without rupture. The cost of a control screening was assumed as the current DRG-tariff for an outpatient ultrasound assessment [DRG code: PG14M [uncomplicated ultrasound scanning] [610 DKK = 81€]].

			2007-€
Fixed cost	Annual equivalent cost (Ultrasound scanner and laptop computer: 35.000€; depreciated over 5 years; 3% real interest))		7,650
Invitation cost	Invitations	7,800 x 1	7,800
	Revised appointments (5.5%)	429 x 1	429
	Reinvitations (16 %)	1,248 x 1	1,248
	Secretary (33 %)	0.33 x 32,214	10,737
	21% overhead		4,245
	Total invitation costs		24,459
Scanning cost	Nurse (80 %)	0.80 x 51,544	41,235
	Doctor	1.00 x 59,600	59,600
	Driving compensation (0.45€/km)	27,013 x 0.45	12,156
	Others (gel, napkins etc)		360
	21% overhead		23,804
	Total scanning costs		137,155
Total annual cost			169,264
Average cost per participants			28,21

Table 5. Annual cost of the screening programme for 6000 scanned persons

4.3.5.2. Costs of treatment

As the Danish DRG tariffs probably are inappropriate classified concerning emergency procedures without rupture and doesn´t include costs before and after the admission to the Vascular Department, a detailed validation study was performed to estimate the costs of operation for AAA in the County of Viborg[304].

The three courses of treatment that was the subject of analysis was defined in relation to the indication of treatment as classified in the national vascular registry called "Karbase" that record all Danish vascular operative and endovascular interventions; [code 3: asymptomatic and planned surgery [EAAA], code 4: acute surgery within a day due to symptoms but without preoperative finding of rupture [AAAA], and code 5: acute surgery because of ruptured AAA [RAAA]].

The "karbase" [www.karbase.dk] was used to identify 25 consequtive cases with each of the three specific interventions performed by the Department of Vascular Surgery at Viborg Hospital by Karkirurgisk Department done before March 2008. The 75 patient records were located and represented the primary source for counting activities and resources.

To illustrate the use of resources, a cost model based on the "activity based costing [ABC]" principle[305] was developed based upon past records, combined with clinical and financial knowledge of such patients, and a database for structured recording of the data was created.

Resources were defined in relation to the course prior to surgery [pre], the operative intervention [s], the subsequent course at the vascular surgical department, shift and hospitalization in other departments and in the outpatient clinics [post] [Table 6].

	Unit costs	Explanation and assumptions
Preoperative outclinic consultation	1,367.00	DRG BG50C, ICD10: I714*
Preoperative outclinic CT scans	1,315.00	DRG PG10C, ICD10: I714*
Prim. dept. receiving emergencies	18,970.00	DRG O550, ICD10: I713*
Operation at primary receiving hospitals	14,000.00	Local agreement of additional hour based salary for two nurses (mean 1000Dkr/hour) and one vascular consultant (mean 1000Dkr/hour) using in average 7 hours away
Operation room (Dkr/hour)	1,500.00	Source: The cost database for Viborg Hospital at the national board of health
Anaesthetic nurse(s)	201.14	Mean hourly salaries. Source: Department of Wage and Staff , Viborg Hospital
Anaesthetic assistant	201.14	
Anaesthetic consultant	428.79	
Anaesthetic senior registrar	350.83	
Vascular consultant surgeon	428.79	
Vascular senior registrar	350.83	
Vascular junior registrar	270.27	
Dacron grafts - Tube Dacron grafts - Bifurcated	2,800.00 3,835.00	Source: Marcom Medical ApS
Intensive care unit (Days)	25,193.00	Source: The cost database for Viborg Hospital at the National Board of Health
Ward days, Vascular Department	5,645.00	
Ward days, Surgical Department	4,719.00	
Consultation at another specialist	175.42	Half an hour salary for a senior registrar Source: Department of Wage and Staff , Viborg Hospital
Gastroscopy (Dkr/examination)	629.77	Costs 192,000 + 100% at least during function time= 384,000. Max. 1200 exam.= 320 Dkr + 143.41 + 166.36¤ Source: Olympus and Specialist practionerer Jan Lindholt
Sigmoideoscopy (Dkr/examaination)	459.02	Costs 162,000 + 100% at least during function time= 224.000. Max. 1500 scopies= 149.33 + 143.41 + 166.36¤ Source: Olympus and Specialist practionerer Jan Lindholt
Coloscopy (Dkr/examination)	1,199.77	Costs 285,000+(½x498,000) + 100% at least during function time= 1,068,000. Max. 1200 scopies= 890 Dkr + 143.41 + 166.36¤ Source: Olympus and Specialist practionerer Jan Lindholt
Abdominal wall mesh (Dkr/piece)	5,000.00	Source: Marcom Medical ApS
VAC dressing (Dkr/piece)	1,500.00	Abdominal dressing kit: 2459.00+canister:277.50+pump leasing: 310.00=3046.50 each time Source: KCI Medical ApS
Dialysis (DKr/hour)	135.00	Exact mean use of utensils for one hour continuous dialysis. Source: Nurse Susanne Fischer, Esbjerg Hospital
Erythrocytes (Dkr/piece)	1,002.00	Exact production prices from the department of immunology, Viborg Hospital. Source: Leading Consultant Kirsten Rissom
Plasma (Dkr/piece)	228.00	
Thrombocytes (Dkr/piece)	1,116.00	
NovoSeven (DKr/dosis)	7,955.00	
Postdischarge iliac PTA	30.823,00	DRG 0523. OP code: KPDP30*
Postoperative outclinic consultation	1,367.00	DRG BG50C. ICD10: I714*
Postoperative outclinic gastroscopy	3,268,00	DRG PG05G. OP code: KUJD02*
Postoperative outclinic sigmoidoscopy	3,855.00	DRG PG05G. OP code: KUJF42*
Postoperative outclinic coloscopy	3,855.00	DRG PG05G. OP code: KUJF32*
Postoperative outclinic X-ray of Colon	3,012.00	DRG PG14 F. Op code: UXRD25*

Table 6. Cost units for the components used in the analysis

***: Diagnosis related group tarif in 2007. Source: http://drgservice.sst.dk/grouper/start.aspx**
¤ : Washing machine costs 236,000 DKr, takes 35 minutes=16 times daily 220 times yearly for 5 years + 130 DKr in utensils per wash= 143.41 per wash. Monitor and lighting resources costs 300,000, are used 7½ times daily, 220 times a year=36.36 per scopy.

Patient resource use was recorded up till 12 months after the first day of admission for AAA surgery. The pre-operative resource includes appraisal of the clinic and CT scan, possible emergency receiving and processing at non-vascular surgical departments. This resource was determined by applying the national 2007 DRG rate O550 of 20,075 DKK [http://drgservice.sst.dk/grouper/], and a local agreement concerning emergency vascular surgery at other hospitals.
The per-operative resource includes costs associated with surgery [time of personnel and operating theater], and the use of different procedures and utensils. Staff time for surgery was determined from a discussion with 2-3 representatives from each of the involved professionals. It was specifically assessed how long each profession uses beyond "knife-time", which emerged from the record [Table 7].

The remaining resources were determined from a simple counting of patient records information.

Post-operative resources included bed-days in intensive care and the wards, supervision from other specialties, and additional surgical procedures [Table 8].

Cost after discharge from the Vascular Department was determined from simple counting and includes treatment of complications in other departments [Table 8], shifts from Viborg Hospital to other hospitals for further processing and finishing, and re-admissions because of AAA surgery-related complications in the form of abdominal pain with no known cause, wound infections, wound rupture, postoperative hernie, stomy-related hospitalizations and ileus.

Unit costs were worth loaded from the 2007 price levels based on various sources. Local unit costs prepared by the hospital department of economics and plan or local agreements were generally preferred. There was a local agreement for costs associated with treating emergency patients at foreign hospitals.

Personnel costs were calculated as the actual wage paid per hour multiplied by a "load-factor" of 1.5 for all personnel. The cost per bed-days in the [vascular] surgical and intensive wards was determined with the locally estimated unit costs in the health costs database hosted by the National Board of Health in Copenhagen. Consumption of equipment and utensils was inserted worth [excluding VAT] in consultation with the relevant supplier. Equipment costs were calculated from the equipment purchase price amortized over life of the assumption of linear depreciation, no scrap value, 3% discounting rate, and measured in relation to assumptions about the annual use.
Overhead also called 'contribution to the common features' was included in the bed fair price but not other costs. For these costs were attributed to an overhead contribution of 21%, as informed by the health costs database.

Costs of emergency call, duty fees, and emergency travel expenses other than the above special agreement were not included.

DRG rates were used for some relative simple and uniform services - especially outpatient contacts because it was the impression that these DRG rates give a good description of the actual costs, especially because there is rarely use of other department´s resources.

As a sensitivity analysis, calculations were performed with the exclusion of three courses of treatment with a number of serious complications and who therefore had very high costs.

Records were available for all included patients. The average age was 71 years with no significant difference between the three patient groups. The average admission time was 9.1, 16.6 and 24.0 days after EAAA, RAAA, and AAAA, respectively. Six patients [24%] died in hospital within the first 48 hours. Further 3 patients died [36%] within the first 30 days after operation for RAAA and 2 within the first 30 days of operation for AAAA [8%], whereas no postoperative deaths were planned after surgery. Table 9 shows the total and average costs for the three types of operation mode. The total expenditure was dominated by days at the intensive care unit and wards. They were between 78% and 81% of the total cost.
The total average cost for the three courses of treatment were 115,551 DKK for EAAA, 259,712 DKK for AAAA and 436,127 DKK for RAAA [p = 0.002]. The cost of the stay at the vascular department was 109,144 DKK [EAAA], 178,813 DKK [AAAA] and 210,158 kroner [RAAA]. Resources used by other departments were 6,407 DKK, 80,899 DKK and 225,969 DKK, equivalent to, 6%, 34% and 56% of total costs, respectively [p <0.001]. Three acute operated patient differd markedly from the others by very long hospitalizations, and multiple interventions in general anesthesia. Common was the use of vacuum assisted wound sealing of the open abdomen with gastrointestinal damage [Table 8]. The cost of these three complex patients was determined to 1.48 mill. DKK, 1.93 mill. DKK and 2.83 mill. DKK, respectively. They constituted 25% and 46% of the total cost for the treatment of RAAA and AAAA, respectively.
If these three special cases was excluded, the average cost to 115,551 DKK 205,846 DKK and 267,682 DKK [p = 0.006]. These costs were used in the final baseline cost effectiveness analysis in study III. However, a sensitivity analysis including the costs was performed. The study is accepted for publication[304].

4.3.5.3. Discussion of costs

4.3.5.3.1. Costs of screening

The cost of the screening was determined as the cost of a permanent screening programme with a maximum capacity of 6000 individuals being screened. The cost of the screening programme was assumed to be 231,000 Euro per year [see Table 5]. The establishment cost included recruitment and training of staff, planning and organisation of the programme and includes financial cost [interest] and depreciation of the necessary equipment. Based upon the experience

		Before procedure	Under procedure	After procedure	Hourly rate(Dkr)	Cumulated costs
Operation room	EAAA	105 min	160.0 min	60 min	1.500	8,125
	AAAA	105 min	153.4 min	60 min		7,960
	RAAA	60 min	152.20 min	75 min		7,180
Two surgical nurses	EAAA	2 x 105 min	2 x 160.0 min	2 x 45 min	191.27	1,976
	AAAA	2 x 105 min	2 x 153.4 min	2 x 45 min		1,934
	RAAA	*(2 x 60 min)*	*(2 x 152.2 min)*	*(2 x 60 min)*		1,735
Anaesthetic nurse(s)	EAAA	105 min	1 x 160.0 min	45 min	201.14	1,039
	AAAA	(105 min)	1 x 153.4 min	45 min		1,017
	RAAA	*(60 min)*	*(2 x 152.2)*	*(60 min)*		1,422
Anaesthetic assistant	EAAA	0 min	1 x 60 min	0min	201.14	201
	AAAA	0 min	1 x 60 min	0 min		201
	RAAA	*(1 x 30 min)*	*(1 x 60 min)*	*(1 x 30 min)*		402
Anaesthetic consultant	EAAA	90 min x 0.5	0.5 x 160.0 min	60 min x 0.5	428.79	1,108
	AAAA	90 min x 0.5	0.5 x 153.4 min	60 min x 0.5		1,084
	RAAA	*(60 min x 0.75)*	*(0.75 x 152.2)*	*(60 min x 0.75)*		1,459
Anaesthetic senior registrar	EAAA	90 min x 0.5	0.5 x 160.0 min	60 min x 0.5	350.83	994
	AAAA	90 min x 0.5	0.5 x 153.4 min	60 min x 0.5		887
	RAAA	*(60 min x 0.75)*	*(0.75 x 152.2 min)*	*(60 min x 0.75)*		1,194
Vascular consultant surgeon	EAAA	0 min	0.5 x 160.0 min	0 min	428.79	572
	AAAA	0 min	0.75 x 153.4 min.	0 min		822
	RAAA	*(30 min x 0.75)*	*(0.75 x152.2 min)*	*(60 min x 0.5)*		987
Vascular senior registrar	EAAA	0 min	0.5 x 160.0 min	0 min	350.83	468
	AAAA	0 min	0.5 x 153.4 min	0 min		673
	RAAA	*(30 min x 0.75)*	*(0.75x 152.2min)*	*(60 min x 0.5)*		808
Vascular junior registrar	EAAA	0 min	1 x 160.0 min	0 min	270.27	721
	AAAA	0 min	1 x 153.4 min	0 min		691
	RAAA	*(30 min)*	*(1 x 152.2 min)*	*(0 min)*		821

Table 7. Peroperative use of staff and time just before, during and immediately after operation until arrival at the intensive care unit for AAA based upon consensus and measured mean time under the procedure among the involved subject divisions and specialities.

First line in cells: planned procedures [EAAA], second cell line: emergency procedures without rupture [AAAA], third line: emergency procedures with rupture [RAAA].

with the trial[102], it was assumed that a permanent programme would require one nurse four days a week, one medical doctor five days a week and a secretary working one third of a full employment with the programme. However, this is a probably not a permanent setup. Doctors are not needed at the screening sessions,- actually nurses could also be replaced by health staff with a shorter education, and it could be discussed whether two persons are required. Consequently, the screening costs may be assumed too high.

4.3.5.3.2. Costs of surgery

The consecutive sampling gave a representative age distribution and 30 days post-operative mortalitet. The sample included 3 patients with serious complications, and particularly high costs. Against the exclusion of these speeches in particular the risk of selection bias,

since their complications are a known part of modern emergency surgery for AAA, and they contributed with 4 and 8% of the included cases acutely operated due to imminent rupture or manifest rupture, respectively. The exclusion of these may have caused selection bias against screening. However, this was deliberately done in order to get a conservative estimate. Endovascular treatment of AAA [EVAR], which is used increasingly in other parts of Denmark, was not included in the study because the Vascular Surgical Department at Viborg Hospital does not use this method [www.karbase.dk]. However, cost analyses has shown that immediate treatment costs are not much different than open surgery; costly endoprostheses are offset by fewer complications and shorter hospitalizations at both intensive care units as well as wards, but a similar estimation of EVAR could be relevant for the generalisation of the results.
There is a risk of information bias. Cost of on duty calls, and emergency transportation are not included. The data registration of the severe wound complications was deficient as either common intervals for redressing were not followed or it just wasn´t recorded in the

At the Vascular Department	EAAA		AAAA		RAAA	
	N=25	N=25	N=24	N=25	N=23	N=25
Gastroscopy			3	3	4	4
Sigmoideoscopy	4	4	5	5	3	3
Coloscopy			1	1	1	1
Tracheostomy			0	1	3	3
ITA supported MR or CT			1	1	3	3
Explorativ laparotomy			1	1	1	1
Hemicolectomy			2	3	3	3
Iliostomy			1	1		
Wound rupture			1	3	4	4
Change of wound dressing				1	1	1
Wound closure					3	3
Bleeding					5	5
Embolectomy	1	1	1	1		
Major amputation			2	2		
Lymphocele	1	1				
Ileus	1	1	1	1		
Dialysis					12	12
VAC Dressings			0	7	11	11
Abdominal wall mesh					1	1
Total number	*7*	*7*	*19*	*31*	*55*	*55*
After the postoperative stay at the Vascular Department						
Gastroscopy			1	2		2
Sigmoideoscopy						1
Coloscopy						
Tracheostomy			1	2		2
ITA supported CT ot MR						3
Explorativ laparotomy						
Hemicolectomy						*3*
Iliostomy						1
Clossure of stomy			2	2	2	2
Wound rupture						1
Change of wound dressing						
Wound closure						1
Bleeding						1
Embolectomy						
Major amputation						
Lymphocele						
Pleural drainage				1		
Ileus				1		1
Iliac PTA			1	1		
VAC Dressings				15		55
Dialysis						20
Total number			*5*	*24*	*2*	*93*
Postoperative outpatient interventions						
Gastroscopy						
Sigmoideoscopy						
Coloscopy						
X-ray of Colon						
Total number of additional interventions	7	7	24	55	59	148

Table 8. Additional procedures after operation for AAA with and without inclusion of outliers [see later].

Preoperative costs	Unit costs (DKK)	EAAA		AAAA		RAAA	
		N	costs	n	costs	n	costs
Preoperative outpatients	1,367	25	34,175				
Preoperative CT scans	1,315	25	32,875				
Prim. dept. receiving emergencies	18,970			11	208,670	25	474,250
Operation at primary receiving hospitals	16,940					3	50,820
Preoperative costs *Mean preoperative costs*			*67,050* *2,682*		*208,670* *8,347*		*525,070* *20,650*
Peroperative costs			*67,050* *2,682*		*208,670* *8,347*		*525,070* *20,650*
AAA operations –staff Operation-room (Dkr/hour)	1,500	25	264,264 193,750	25	260,839 189,625	25	341,226 171,125
ITU (days)	19,902.47	43	855,806	96	1,910,637	119	2,368,394
Ward (days)	4,459.55	173	771,502	159	709,068	92	410,279
Inspection by other speciality	263.13	4	1,053	29	7,631	34	8,946
Additional procedures		7		31		55	
Staff Operation-room (Dkr/hour)	1,500		32,798 4,875		371,402 60,000		477,197 56,650
Utensils and other expenses							
Grafts							
Gastroscopy		25	81,605	25	79,495	25	83,715
Sigmoideoscopy	629.77			3	1,889	4	2,519
Coloscopy	459.02	4	1,836	5	2,295	3	1,377
Erythrocytes	1,199.77			1	1,200	1	1,200
Plasma	1,002	44	44,088	74	74,148	249	249,498
Thrombocytes	228	2	456			48	10,944
NovoSeven	1,116					9	10,044
Dialysis	7,955					9	71,595
Mesh	3,240					12	38,880
VAC Dressings	5,000			1	5,000	1	5,000
21% overhead	3,046.50			7	21,326	11	33,512
Costs at the Vasc. Dept.	0.21		473,557		775,840		911,841
Mean costs at Vas. Dept			*2,728,590*		*4,470,315*		*5,253,942*
Postdischarge costs							
ITU (days)	19,902.47			43	855,806	145	2,885,858
Ward (days)	3,728.01	13	48,464	115	428,721	230	857,442
Inspection by other speciality	263.13	1	263	5	1,316	20	5,263
Additional procedures							
Staff Operation-room (Dkr/hour)	1,500				48,585 25,625		150,478 70,500
Utensils and other expenses							
Gastroscopy	629.77			2	1,260	2	1,260
Sigmoideoscopy	459.02					1	459,02
Iliac PTA	30,823			1	30,823		
VAC Dressings	3,046.50			15	45,698	55	167,558
Dialysis	3,240					20	64,800
Abdominal wall mesh	5,000			1	5,000		
21% overhead	0.21		10,233		302,995		882,760
Costs at other Dept.			*58,960*		*1,745,829*		*5,086,379*
Mean costs at other dept.			*2,358*		*69,833*		*203,455*
Outpatient costs							
Outpatient contacts	1,367	25	*34,175*	42	*57,414*	22	30,074
Gastroscopy	3,268						
Sigmoideoscopy	3,855			1	3,855		
Coloscopy	3,855			1	3,855	2	7,710
Rtg of Colon	3,012			1	3,012		
Total outpatient costs			*34,175*		*68,136*		37,784
Total postdischarge costs			*1,367*		*2,725*		*1,510*
Total costs **Mean total costs** (Mean total costs -outliers)			2,888,775 **115,551** (115,551)		6,492,950 **259,718** (205,846)		10,903,175 **436,127** (267,682)

Table 9. Costs at the Vascular Department in 2007 for treatment of AAA.

EAAA	DRG code	2002	2003	2004	2005*	2006	2007	2008	2009
DRG tariffs	0515	80,528	91,352	64,771	74,336	88,016	100,339	111,177	117,331
Estimated costs							115,551		
Estimated vascular[1] costs during admission at vascular department							109,144		
RAAA									
DRG at death witin 48 hours	0513	34,495	59,075	60,679	39,874	48,588	47,405	60,862	60,918
Estimated costs of death witin 48 hours							72,665		
Estimated costs during admission at vascular department and death witin 48 h							52,015		
DRG without death within 48 h	0514	134,887	193,292	194,501	125,348	108,554	114,092	123,151	251,897
Estimated costs without death within 48h +/- incl. of outliers							550,905 336,512		
Estimated costs during admission at vascular department with and without death within 48 h +/- outliers							269,490 270,168		

Table 10. Estimated costs [DKK] and Danish DRG tariffs from the introduction of DRG tariffs for AAA repair in 2002

*** : In 2005, costs for complicated courses at intensive care units were separated from DRG tariffs: 0513 og 0514 as independent DRG groups [www.sst.dk/Planlaegning_og_behandling/DRG/Takster.aspx] and [www.sst.dk/upload/an%C3%A6stesiologi_og_intensiv_medicin_notat.pdf].**

2632 Intensiv group I: Simple organ failure of one or more organs
2633 Intensiv group II: Increasing serious organ failure of one organ
2634 Intensiv group III: Increasing serious organ failure of more organs
2635 Intensiv group IV: Serious multiorgan failure
1: during admission at the vascular department

Finally, a standard bed tariff was used, but complicated cases require more personnel and other resources than the simple, uncomplicated cases. These potential biases of information means that the cost of emergency operations is being underestimated compared to planned interventions, which were mainly complication-free.
Comparison with other studies is difficult, but excluding these outliers from the analysis, the estimated ratio of costs for ruptured versus planned repair of about 2.0 compares very well to the numerous of studies made in the past[192;306-311], although four times higher costs of ruptured cases have been reported as in our survey[304;312]. However, most publications are from the nineties. Since then, there has been a paradigm shift in several areas; cross laparotomy is now the standard for planned operationer since they are associated with fewer pulmonary complications, fewer wound ruptures and postoperative ventral hernias, but quick laparotomy through the mid line remains the preferred method for emergency operations[313]. Also introduced is abdominal decompression when symptoms of abdominal compartment occur and vacuum assisted wound closure for large open abdominal wounds[192;197;306-309;314;315]. It might be what is reflected in the 2009 DRG rate which has experienced a marked increase among the survivors to 251,897 DKK.
Comparing the estimated total costs with the current DRG-tariffs for 2007 have predominantly good agreement concerning planned operations and the operation of rupture with death within 2 days [Table 10].

For acute operations, the actual estimated costs were 2-4 times higher than the DRG rate. This was initially considered to be caused by the DRG rate does not include costs outside the admission to the vascular department. However, the calculated costs at the vascular department are more than twice as high as the DRG tariffs [Table 10]. A clinically unexplained and drastic reduction of costs for survivors of rupture occurred in 2005 and the subsequent years until 2009. Consequently, the previous year's of DRG-related validation work was reviewed. It revealed that in light of the recommendation from the Danish Society of Anesthetics and Intensive Medicin , 4 independent DRG tariffs [2632-2635] for intensive treatment for complicated cases based on severity of organ failure was established in 2004*. Uncomplicated cases with less than 24 hours of stay in intensive sections are not

included in these. Intensive costs of complicated cases that are more the rule than the exception at rupture, is thus no longer included in the DRG charges in 0513 and 0514 from 2005. In 2009, however, it was chosen not to reduce the cost to limit seasonal variations and change the criteria for intensive-DRG groups, where the limit was previously at> 48 hours and to> 72 hours. This has lead to the first 3 days of intensive costs are contained in the RAAA-DRG rate O514.

However, the sharp increase in 2009 DRG rate among survivors of rupture to 251,897 DKK does not include costs for hospitalization in the intensive care section beyond 72 hours. This has implications for the costs of complicated cases and may be part of the explanation for the high estimated costs at 436,127 DKK in our study. Overall; the comparison gives rise to the conclusion that DRG tariffs 0513 and 0514 do not provide a sufficient description of the total costs of treatment of AAA. The lack of inclusion of resources before and after vascular hospitalization costs and the lack of intensive treatment costs leads to a significant underestimation of resource use in the treatment of RAAA and AAAA.

In addition, the basic principle of DRG system that each DRG group should be homogeneous is not satisfied with the existing classification. AAAA is associated with more complications and higher mortality than EAAA and the current study shows that there is a considerable difference in resource use. Use of the existing DRG tariffs in a health economic evaluation of a screening program, as in the Danish HTA report[316] can lead to a serious bias that underestimates the costs of resource use and the impact of screening.

The current detailed study of the costs of surgery indicates that resources for treatment of AAA is significantly undervalued and calculations with more accurate costs can influence the outcome of whether a Danish screening program for AAA is cost effective or not. As the Danish DRG tariffs are inappropriate classified and doesn´t include costs before and after the admission to the Vascular Department, as well as all costs at the intensive units, the results of the study to estimate the costs of operation for AAA in the County of Viborg were used in the Study III.

4.3.6. Statistical analyses

The data were analysed as intention-to-treat from the time of randomisation. This means that the analysis compares those who were randomised to the control group with those in the intervention group and no exclusions were made due to non-attendance. A per-protocol analysis where the control group is compared with those who attended the screening programme was made as a sensitivity analysis.

All cause mortality and AAA related mortality was compared for the two groups using Cox-regression analysis.

Difference in mean life-time [days] from randomisation until death or 31 March 2008 was estimated. The time from randomisation until an AAA related [acute] operation was calculated and compared between the two groups by Cox´s regression analysis, and the 30-days post operative mortality calculated.

4.3.6.1. Quality adjusted life years

Quality adjusted life years were estimated for each individual assuming that the average quality of life at the time of randomisation was similar to that of a national representative Danish sample. In the absence of reliable quality of life information for the randomised sample, it was assumed that the sample had similar EQ-5D index scores as a national representative sample[317]. Consequently, it was assumed that quality of life naturally deteriorates with age similar to the difference observed in the national sample of men aged 65 and older [quality of life is assumed to deteriorate with 0.00485 per year over 65][317].

When patients experience an elective AAA operation it was assumed that they experience a temporary reduction in quality of life of 0.05 during a six month period and then returns to the same level as the same age group of the representative sample. A patient who experienced an acute AAA operation without rupture was assumed to suffer a loss in quality of life of 0.10 during the subsequent six month period, and patients with an acute AAA operation and rupture suffer a loss of 0.15 during the subsequent 6 mounts.

The net present value of the quality adjusted life year [until death or 31 March 2008] was compared for the two groups.

4.3.6.2. Health care costs

The health care cost during the time from randomisation until death or 31 March 2008 was estimated for each individual based on the recorded events. The considered events were:

1] invitation to the screening programme,
2] attendance in the screening programme,
3] subsequent control screening [for those at increased risk of AAA [aortic diameter 3-5 cm]],
4] referral to vascular outpatient clinic,
5] planned operation,
6] acute operation with rupture,
7] acute operation without rupture.

The cost was discounted to the net value at the time of randomisation based on the recorded event date.

Incremental cost-effectiveness ratios were calculated for life years gained and QALYs gained.

4.3.6.3. Subgroup- and sensitivity analyses

A subgroup analysis was performed concerning the 65 year old men, since permanent programmes are expected to use this age group as group of target. Another subgroup analyses were performed concerning men in high and low risk for AAA – defined

as illustrated in table 4, respectively. Sensitivity analyses were performed by treatment costs observed by inclusion of the above mentioned outliers and by different discount rates.

4.4. METHODS USED IN STUDY IV

4.4.1. Diagnosis and follow up of men with a screen-detected small AAA

The men were diagnosed by the screening methods described in 4.1.1. Men with a small AAA of 3-4.9 cm were offered annual follow-up for aneurysmal expansion, and refered for preoperative evaluation, if the AAA became 50 mm or more in diameter. Death and operations were identified as described in 4.1.3.

Admissions to hospital before and after AAA diagnosis were identified and classififed as described in 4.3.4.

4.4.2. Estimation of the degree of calcification of the aneurismal wall

All the patients with a screen-detected AAA in 1994 consulted the trial doctor for information, examination and a rescan. During this scan, the degree of calcification was evaluated by a cross sectional view at the maximal diameter. No standardised method was used, and the degree of calcification was judged to be above or below 50%. The judgement was hidden by storing electronically. In 32 cases, the trial doctor diagnosed the AAA initially, judged the degree of calcification at this diagnosis and repeated the judgement when the patient came for the baseline consultation. An intraobserver reproducibility of 84% [95% C.I. 70-93%] was calculated, but the method has not been evaluated between observers.

4.4.3. Models for calculating expansion rate

The mean annual expansion rate of small AAAs was described to be about 2.5 mm annually, and in case of a variability of the measurement as high as 5 mm, we would need an unrealistically large sample size to detect modest predictors of expansion. We ascribe the variability of the measurement partly to the lack of a standardised method, the number of observers and the number of scanners. A strict standard for measuring the maximal aortic AP-diameter was therefore introduced: The right-angled measurements were done in a longitudinal view. Prints were made to demonstrate the visualised morphology and where the AAAs were measured. Measurements were performed in an intramural-intramural way, from plaque to plaque, if possible in order to prevent variations in luminal-intramural-extramural measure points and sources of error. The luminal source of error is the presence of a mural thrombus, and the extramural source is the anterior longitudinal ligament or the vertebras themselves. All positive findings were rescanned by the present doctor of the trial which limited the number of observers to one to three over twelve years of follow up and only one scanner was used.

The expansion rate in study IV and V was calculated as the change in the AP diameter from the first to the last measurement divided by days, and transformed into annual units[239]. However, in theory, this method does not optimally adjust for variability of the measurements and the different numbers of observations and different observation periods. Recently, we therefore used a linear mixed effect model for calculating the individual expansion rate as the individual linear regression coefficient based on the available observations [not yet published]. We assessed the annual expansion rates of the AAAs as the slope of the linear regression line of AAA-diameter versus time. In order to account for the different number of observations per patient, a linear mixed effect model was fitted. The random effects were the regression coefficients of the linear regression. Thus each patient had his own intercept and annual growth rate. The fixed effects were the annual expansion rates for the independent variables.

This seems to be the optimal way to calculate expansion rate in theory, but whether it has any impact is unknown. The Spearman's correlation coefficient [rho] between the crude expansion rates calculated by the two methods was 0.95 [p<0.001, Figure 5], and the mean difference was 0.0083 mm/year [95% C.I.: -0.0831; 0.0669. paired t-test; P=0.831 [Unpublished data].

A Bland-Altmann plot of the mean expansion rate of the two methods and the difference between the two methods showed that the variation seemed equally distributed around zero – perhaps with a tendency for the fixed effect model to yield higher growth rates in slowly progressing AAAs and slower growth rates in rapidly expanding AAAs [Figure 6].

Figure 5. Comparison of mean annual AAA-expansion rates estimated by a simple substration method or a mixed effect method

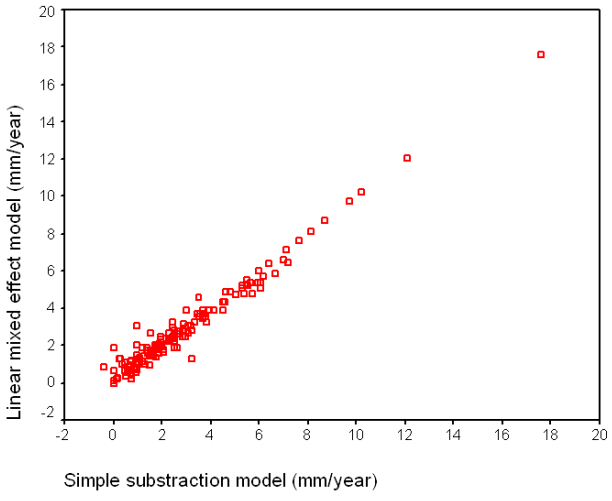
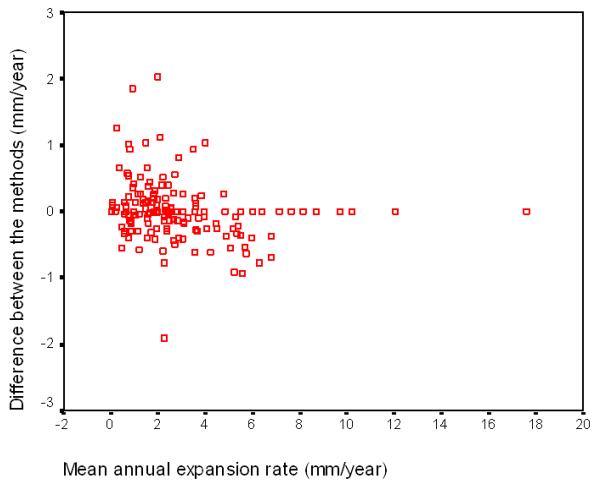


Figure 6. A Bland-Altmann plot of the mean expansion rate of the two methods and the difference between the two methods



The difference between the two methods would hence seem to be small. However, the fixed effect estimated mean expansion rate correlated more closely with the initial maximal AAA diameter than the rate estimated by the simple substraction method [rho=0.50 vs. rho=0.43], but the growth rate difference among smokers and non smokers was larger when estimated with the simple method than with the fixed effect method [1.49 mm/year [95% C.I.:0.67; 2.30, P<0.001] vs. 1.32 mm/year [95% C.I.; 0.53; 2.11, P=0.001]].

Before using a linear model, an exponential model was considered because a retrospective study of 56 cases with AAAs or thoracic aortic aneurysm found that exponential models of expansion had a slightly better fit than linear models[318].

However, in our cohort of cases with small AAAs, an exponential model did not seem to fit better than a linear model in the mixed effect model [data not shown].

4.4.4. Statistical analyses

Chi square tests were used to test dichotomous variables. Wilcoxon's rank sum test for unpaired data was used to compare expansion rates, among cases with more or less than 50% calcification in the aneurismal wall.

Initial AAA size and expansion rate were logaritmised and used in multivariate linear regression analyses as dependent variables adjusting for age, smoking and aspirin use. Cox's proportional hazards regression without and with adjustment for age, current smoking and aspirin use was used to compare operation, first cardiovascular event after AAA diagnosis, and mortality rates for AAA between cases with more or less than 50% calcification in the aneurismal wall.

4.5. Methods used in Study V

4.5.1. Diagnosis and follow up of men with a screen-detected small AAA.

The methods were similar to the methods described in 4.4.1

4.5.2. Models for calculating expansion rate

The expansion rate was calculated as the change in the AP diameter from the first to the last measurement divided by days, and transformed into annual units [See 4.4.3].

4.5.3. Serological analyses

Some of the initial planned serological analyses for the established bio bank, like the measurement of elastase-alpha-1-antitrypsine complexes, need a much standardised method[249]. We could not assume that ordinary technicians would respect this and therefore had to do it ourselves. Furthermore, in order to reduce the round-the-clock variations of the various serological parameters, all samples were drawn and prepared between 9.00 a.m. and 12.00 noon by the screening team. It was not possible to incorporate this serological procedure into the routine daily screening sessions, so sampling days were arranged within ten days of the initial scan. Only subjects living less than 30 km from the hospital were asked to attend blood sampling. Two subjects refused the sampling. In all, 112 men with AAAs below 50 mm had blood samples taken in 1994. Their age, smoking habits and initial AAA size did not differ from those with an AAA below 5 cm who had not blood samples taken. The plasma samples were stabilized with EDTA and left at 18oC for 45 minutes before centrifugation. Serum and plasma samples were then stored in multiple aliquots at -700 C until analysis. Economic resources were limited and we therefore drew random samples of blood samples from the cohort for various studies. Seventy samples were randomly drawn for study V.

Since it is impossible to obtain AAA wall samples in conservatively treated cases, blood samples provide a pragmatic mini-invasive opportunity to identify factors that influence the aortic matrix metabolism, using the expansion rate and cases expanding to operation-demanding sizes as outcome variables. One of the disadvantages of this approach is that the measured concentrations reflect the total body metabolism; however, this disadvantage is less important for homocysteine and lipids. Another disadvantage is that, except for antibodies, the sample reflects only the period around the sampling time. Various periodic conditions that may influence the wall degradation could include heavy smoking periods and systemic inflammation.

4.5.3.1 Plasma urokinase-like-plasminogen activator [uPA]

P-uPA was measured with the ELISA "Imulyse uPA" from Biopool Int., Umeå, Sweden. The within- and between-assay coefficients of variation were 5% and

9%, respectively. The P-uPA detects free single- and two-chain uPA and uPA in complex with its inhibitors[319]

4.5.3.2. Plasma tissue-type-plasminogen activator [tPA]

P-tPA was measured with the ELISA "Imulyse tPA" from Biopool Int., Umeå, Sweden. The within- and between-assay coefficients of variation were 8% and 10%, respectively. The P-tPA detects free single- and two-chain tPA and tPA in complex with its inhibitors[320].

4.5.3.3. Plasma plasminogen-activator-inhibitor-1 [PAI-1]

P-PAI-1 was measured with the ELISA "Imulyse PAI-1" from Biopool Int., Umeå, Sweden. The within- and between-assay coefficients of variation were 5% and 9%, respectively. The P-PAI-1 detects latent and active PAI-1, but poorly complexes with uPA and tPA[321].

4.5.3.4. Plasma macrophage inhibiting factor [MaIF]

MaIF levels in serum were measured blindly with a routine MaIF-specific sandwich ELISA using recombinant human MaIF as standard[322]. The between-assay coefficient of variation was 18.5%.

4.5.3.5. Plasma tumour-growth-factor-ß1 [TGF-ß1]

Serum TGF-ß1 levels were determined using the TGF-ß1 ELISA kit according to the manufacturer [BioSource International, Camarillo, CA]. Unfortunately, the between-assay coefficient of variation reached 28%, making type II errors very likely.

4.5.3.6. Plasma homocysteine

P-Homocysteine was analysed using gas chromatography-mass spectrometry after reduction with dithiothreitole. Deuterated homocysteine was used as internal standard. The inter- and intra-assay coefficients of variation of the P-tHcy measurements were 5% and 3%, respectively, as assessed by internal and external quality assessment[323].

4.5.3.7. Serum IgA-antibodies against Chlamydia pneumoniae [IgA-CP]

The microimmunofluorescence [MIF] test is considered the "gold standard" for laboratory diagnosis of acute and chronic Chlamydia pneumoniae infection. The MIF test that was used in study V was based on a C. pneumoniae antigen from Washington Research Foundation [WRF]. It is specific for the species and allows detection of the various immunoglobulin types against C. pneumoniae. The test requires highly skilled personnel for the microscopy, and subjective reading of the results is needed.

The laboratory at Statens Seruminstitut [the Danish State Serum Institute] measuring the antibodies against C. pneumoniae have validated the technique: The performance of the MIF test was compared with that of the assays from Labsystems [LAB] and MRL Diagnostics [MRL] by investigation of sera from three groups of patients: group I, 83 sera from 28 patients with atypical pneumonia; group II, 37 sera from 16 patients with acute C. pneumoniae or Chlamydia psittaci respiratory tract infection confirmed by PCR or culture; group III, 100 sera from 100 persons enrolled in the Copenhagen City Heart Study. The concordance in detection rates for IgA antibodies in sera from patients with acute infections reached an acceptable 88%, and in sera from group III, it was 97%. Determinations of endpoint titres were reproducible with <1 dilution step difference for all three methods. Although the three assays used different C. pneumoniae strains as antigens, the detection rates and IgA endpoint titres were similar[324].

4.5.3.8 Serum Cotinine

S-Cotinine was determined by a commercial radioimmunoassay [Diagnostic Products Corp., LA, USA] modified as suggested by Perkins et al[325]. The between-assay coefficient of variation was 5.4%.

4.5.3.9 Serum creatinine and creatinine clearance

The renal function was determined by creatinine, age and weight. Serum creatinine was analysed using the Vitros CREA slide on the Vitros 950 Chemistry System [Ortho-Clinical Diagnostics, Rochester, NY, USA], while the creatinine clearance was estimated by the Cockroft-Gault formula: [[140-age][weight[kg]/[0.825[S-creatinine[micromol/l]]][326].

4.5.4. Statistical analyses

Wilcoxons non-parametric test for unpaired data was used to compare cases expanding above and below 2 mm annually in order to make an analysis comparing certainly expanding cases with stable not with certain expanding cases. Spearmann´s correlation analyses were used to correlate the parameters with uPA, tPA and expansion rate. To correct for the possibility of chance findings, the P-values in table 1 and 2 concerning the same topic were multiplied and divided with the total number of statistical tests.

Finally, logarithmic transformation of S-Cotinine was performed in order to make a multiple regression analysis concerning tPA and expansion rate adjusting for smoking.

4.6. METHODS USED IN STUDY VI

4.6.1. Purification of serum antibodies against the outer membrane protein [OMP] of Chlamydia pneumoniae

Sera were taken from 5 patients with a small AAA, an IgA titre above 64, and an IgG-titre above 128. The patients took part in one of our previous studies on the correlation between the progression of lower limb atherosclerosis, the clinical course of AAA, and

antibodies against C. pneumoniae[294;296;327]. The sera were applied to a new commercially available ELISA test from Labsystems [LOY-EIA]. The LOY-EIAs for IgG-Cp and IgA-Cp are indirect solid-phase enzyme immunoassays with C. pneumoniae OMP as immobilised antigen[296].

We recently evaluated this new fully automatic commercially available ELISA[296], and found high concordance between the results obtained by the new ELISA method and the conventional MIF test for detection of S-IgA and S-IgG antibodies against C. pneumoniae. This high concordance indicates that both tests are measuring the same antibodies. However, it is not possible to assess whether the tests, in fact, also detect a C. pneumoniae infection, because no test is yet able to ascertain whether an individual is or has been infected with C. pneumoniae, i.e. no true reference standard exists[278;279;328]. The correlation between demonstrating C. pneumoniae DNA or antigen in tissue from aneurysms and the antibody titres in serum is controversial[280;281]. It is, however, assumed that IgM antibodies are not detectable in reinfections and persistent infections[280;281], for which reason we assessed only IgA and IgG antibodies.

Isolation and purification of specific antibodies against Cp OMP were as follows; 100 µl of serum sample was diluted 1:2 in PBS buffer [2.7 mM KCl, 1.8 mM KH2PO4, 10.1 mM Na2HPO4, 140 mM NaCl, pH 7.4] and added to the wells coated with C. pneumoniae OMP. The plates were incubated at 37 °C for 1 hour during gentle shaking and washed 10 times with PBS. The purified antibodies were eluted by adding 100 µl elution buffer [0.1 M glycin, pH 3.0] to each well. The eluates were collected and quickly neutralized to pH 7.4 with 1 M Trizma base, pH 9.0.

4.6.2. Proteomic analysis

AAA wall samples were studied on 17 patients undergoing infrarenal AAA repair at the Department of Vascular Surgery, Viborg Hospital. Full AAA thickness tissue was harvested in a standardized way from the central part of the anterior wall of the aneurysm at the maximal dilatation and stored immediately at -22 degrees Celsius. Approximately 1 g was rinsed three times with PBS for 10 minutes. The specimens were crushed in a 1-ml cold sucrose buffer [300 mM sucrose, 10 mM Tris at pH 7.4], containing the protease inhibitors 1 mM Na-EDTA, 1 mM PMSF, 1 [M pepstatin and 1 [M leupeptin, by an Ultra-Turax homogenisator.

Cell debris was removed by centrifugation [14.000 x g for 20 minutes]. Clear protein solutions were used for subsequent gel electrophoresis.

4.6.2.1. Gel electrophoresis and immunoblotting

The total AAA protein content of each sample was estimated by Bio-Rad Protein Assay [Hercules, CA] based on the method of Bradford[329].

For one-dimensional gels, approximately 25 µg of prepared sample was loaded in each well and run on 10-20% gradient polyacrylamide minigels [NOVEX, San Diego].

For two-dimensional gels the serum was dissolved in lysis buffer. Rehydration buffer was added and first dimension was run with IPG strips [3-10NL] from Amersham Biosciences. The second dimension was performed on home-made polyacrylamide gels [12%T, 3%C] that were fixed in 50% [v/v] methanol, 12% [v/v] acetic acid, 0.0185% [v/v] formaldehyde for at least 1 hr or overnight.

They were then washed 3 times for 20 min. in 35% [v/v] ethanol, pre-treated for 1 min. in pre-treatment solution [0.02% [w/v] Na2S2O3,5H2O] and rinsed 2 times for 3 min. in water. Staining of gels was performed for 20 min. in 0.2% [w/v] AgNO3, 0.028% [v/v] formaldehyde after which they were rinsed 2 times for 20 sec. in water. Development was carried out in development solution [6% [w/v] Na2CO3, 0.0185% [v/v] formaldehyde, 0.0004% [w/v] Na2S2O3,5H2O] for approximately 3 min. and was stopped in stop solution [50% [v/v] methanol, 12% [v/v] acetic acid]. Finally, the gels were dried between cellophane sheets and sealed in plastic bags.

From one- and two-dimensional gels, proteins were transferred to nitrocellulose membranes that were blocked for 1 hour with 0.5% skimmed milk and 0.05% Tween-20 in PBS and incubated at room temperature for 1 hour with pure anti-OMP antibody [1:100] isolated from patient sera as described above.

The blots were washed and reacted with horseradish peroxidase-conjugated secondary antibody [sheep anti-human antibody from the LOY-EIA ELISA kit] diluted 1:1000. The bands were visualised by using enhanced chemiluminescence [ECL] kit and ECL hyperfilm [Amersham Pharmacia Biotech, UK].

4.6.2.2. Protein identification

Protein spots were excised from silver stained two-dimensional gels and digested using the protocol described by Mann et al[330]. Briefly, the gel spots were washed with 50 mM NH4HCO3/acetonitrile [1:1] followed by dehydration with acetonitrile. The proteins were reduced in 10 mM dithiotreitol [DTT]/50 mM NH4HCO3 for 1 hour at 56oC, and alkylated in 55 mM iodoacetamide/50 mM NH4HCO3 for 2 hours at room temperature. The gel pieces were washed several times in 50 mM NH4HCO3 followed by dehydration with acetonitrile. The proteins were digested overnight with trypsin [Promega, modified trypsin] at 37 oC and the resulting peptide mixtures analysed by tandem mass spectrometry [MS/MS] at Alphalyse A/S [Odense, Denmark]. The peptide masses obtained were used to query the NRDB sequence database for protein identification. The NRDB database contains more than 360,000 entries and is maintained and updated by EMBL [European Molecular Biology Laboratory]. It was specifically tested whether the proteins could be fragments of C. pneumoniae OMP.

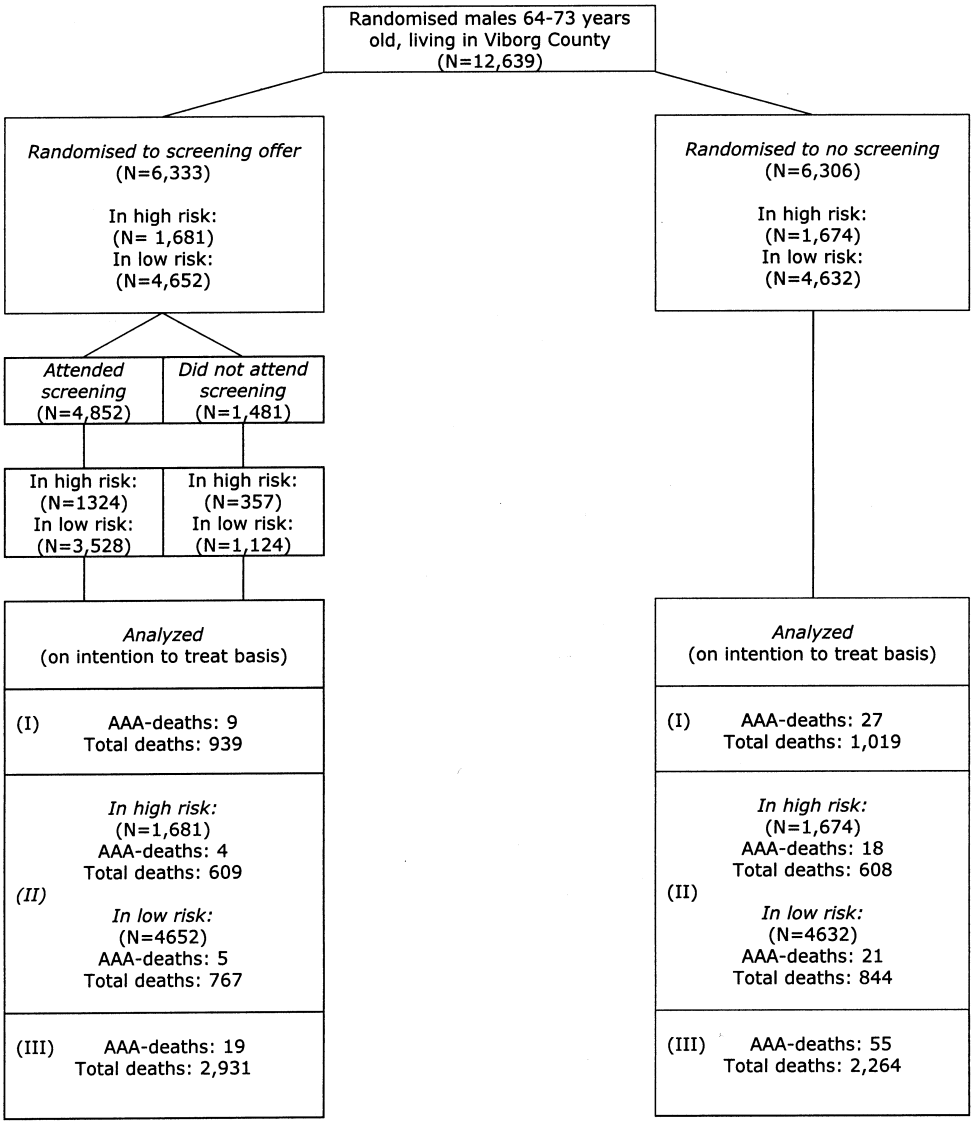


Figure 7. Flow-chart concerning the Viborg randomised screening trial for AAA classified according to pre-existing hospital admissions due to AAA-related disease [high risk] or not [low risk], and time of effectiveness analysis [I,II,III,VII].

4.7. METHODS USED IN STUDY VII

4.7.1. Diagnosis and follow up of men with a screen-detected small AAA

The men were diagnosed by the screening methods described in 4.1.1. Men with a small AAA of 3-4.9 cm were offered annual follow-up for aneurysmal expansion, and refered for preoperative evaluation, if the AAA became 50 mm or more in diameter. Death. Admissions to hospital before and after AAA diagnosis were identified and classififed as described in 4.3.4.

4.7.3. Morbidity classification

The methods used were similar to those described in 4.3.4. [See table 4]

4.7.2. Identification and classification of deaths

Deaths were identified in the Danish Civil Register. Leading and participating causes of death occurring between the enrolment date and 31.12.1999 were obtained from the national Registry of Causes of Death. Using the ICD-10, we classified causes of death as cardiovascular [ICD-10 codes starting with I] or pulmonary [ICD-10 codes starting with J].

4.7.4. Statistical analyses

Among the men screened for AAA, we compared overall mortality for those with and without AAA detected. We used Cox's proportional hazards regression without and with adjustment for age and previous hospitalisation for pulmonary or cardiovascular diseases. We then examined pulmonary

and cardiovascular mortality separately for men with and without previous hospitalisation for those diseases.

Kaplan Meier plots were produced for graphical illustration and used to judge whether the assumption of proportional hazards were present. Finally, we calculated absolute risk and absolute risk difference for death by these causes.

4.8. Materials used in the studies

The material used in the studies was mainly from the randomised screening trial in Viborg County, but in the proteomic analysis [VI], AAA wall samples were studied on 17 patients undergoing infrarenal AAA repair at the Department of Vascular Surgery, Viborg Hospital regardless of whether they had been diagnosed by screening or not.

In the screening trial, 12,639 men with a mean age of 67.7 years were included in the study. No differences in observation length and age upon inclusion were observed between the screened group and the control group. Measurement of the maximal aortic diameter was successful in 4,816 [99.3%] of 4,852 attenders of whom 191 [4.0%; 95% CI: 3.4%-4.6%] had an AAA. Twenty-four men [0.5%; 95% CI: 0.3%- 0.7%] with an AAA above 5 cm in diameter at diagnosis were referred for surgery.

The rest were offered annual control scans. Among these 167 men, 14 [8.3%; 95% C.I.: 4.9-13.3%] never appeared for follow-up, mainly due to death or development of serious co-morbidity.

During the first five years after the initial screening, another 22 men were referred for elective surgery due to expansion, and 9 had died due to AAA in the invited group compared with 27 in the control group. After fourteen years, 84 have been operated electively in the invited group compared with 89 in the control group, 19 had died of AAA in the invited group compared with 55 in the control group [III, Figure 6].

Due to long delays and uncertainty as to when the National Registry of Causes of Death could deliver relevant data, a preliminary study based on regional hospital registries was conducted in 2002 in order to evaluate the hospital-based benefits. It showed a 68% [41-89%] lower risk of dying of AAAs at hospitals in the Viborg County than in the rest of Denmark[298]. When data on causes of death became available, they showed that 19 patients had already died at the date of randomisation, so they were deleted from the analyses.

PART V. RESULTS AND DISCUSSION OF MAJOR FINDINGS

5.1. HOSPITAL-BASED MASS SCREENING OF DANISH MEN AGED 64-73 FOR AAA AND AAA RELATED MORTALITY AFTER FIVE YEARS [STUDY I]

5.1.1. Major findings

We found [I,II] that 12,639 had been randomised, 76.6% attended screening. Among attenders, 4% had an AAA. These men were followed for a mean of 52 months [I]. We found [I] that the screened group underwent 75% [34% to 91%] fewer emergency operations than the control group [P<0.001]. Deaths due to AAA occurred in nine patients in the screened group and 27 in the control group. The number needed to screen to save one life was 352. Consequently, the AAA-specific mortality ratio was 0.33 [0.16-0.71, p=0.003] in favour of screening [Figure 7]. So, screening significantly reduced AAA-related mortality by 67%.

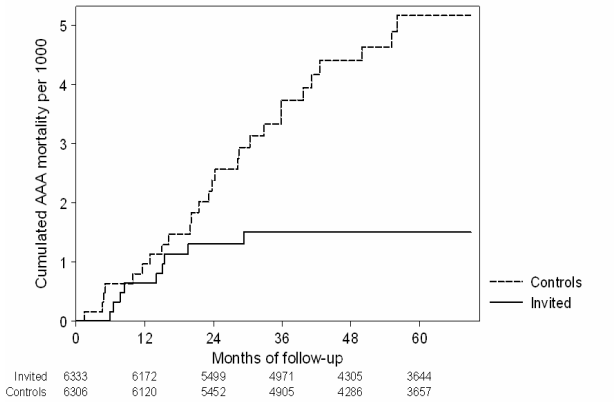


Figure 7. Five-year Kaplan-Meier estimates of mortality from AAA. Screening group and control group [I].

Surprisingly, the all cause mortality was reduced by 8% in the invited group - allthough non-significantly [P=0.053 [log rank test]], Figure 8].

At re-screening after 3-5 years we found that none of the men with an initial normal aorta had developed AAAs. Among those who initially had a 25-29 mm wide aorta, 28.5% had developed AAAs. The incidence of AAA was estimated to 2.6 per 1000 observation years.

We found an incidence of ruptured AAA in the control group of 1.07 per 1000 observation years; and the incidence of AAA-related mortality was 1.04 per 1000 observation years.

A prediction model was created to calculate the expected number of life years gained within 5, 10, and 15 years for two hypothetical cohorts representing screened participants and controls [method in section 4.1].

In the cohort representing the screened participants, we assumed the mortality for the period 1.5 to five years after randomisation to be reduced by the difference in specific mortality due to AAA per 1000 years in the study [0.89, 95% confidence interval 0.40 to 1.37]; before 1.5 years and after five years we assumed that the mortality was unaffected by screening. In other words, if there would be no additional lives saved after a median of 52 months, 32 [95% C.I.: 14 to 49] life-years would be saved after 5 years, 107 [95% C.I.: 48-164] after 10 years and 158 [95% C.I.: 71-243] after 15 years.

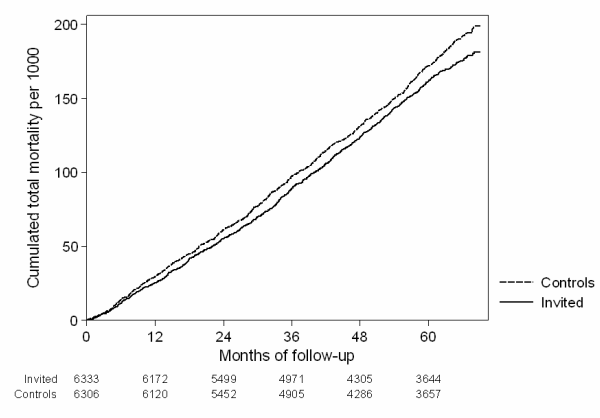


Figure 8. Kaplan-Meier estimates of total mortality in Danish men aged 64-73 years screened for AAA and controls.

Finally, the mortality among non-attenders to screening was significantly higher than the mortality among attending men [P<0.001, Log rank test, Figure 9].

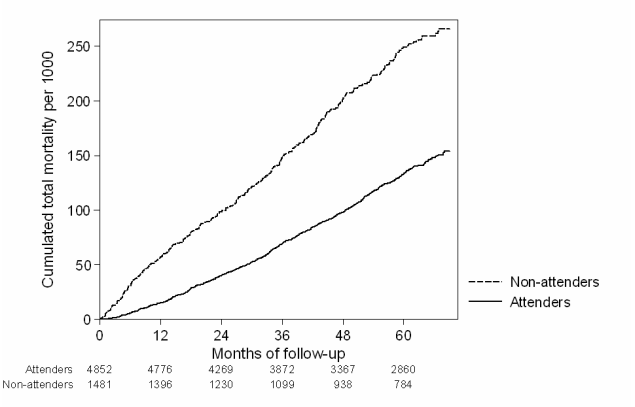


Figure 9. Kaplan-Meier estimates of total mortality among attenders and non-attenders for screening for AAA.

5.1.2. Discussion of major findings in study I

5.1.2.1. Benefits of screening

Four randomised trials have been conducted to estimate the potential benefit of screening. The first started in Chichester [UK] in 1989 by enrolling 65-80-year-old men and women[42;331;332]. Causes of death were obtained from a local registry and later from the national registry. AAA-related deaths were reviewed by one doctor. Whether this doctor was blinded to knowledge concerning intervention group is unknown.

Among men, 6,433 were considered for randomisation, but 373 were excluded due to illness. The attendance rate was 73%, and 7.6% of these had an AAA. After five years, a statistically insignificant 41% reduction in AAA-specific mortality was noted[331].

After 10 years, the mortality rate was 21% lower in the invited than in the control group. The benefit peaked after 4 years with a mortality rate ratio of 48%; hereafter, the mortality was almost equal in the two groups[332]. After 15 years, the benefit had decreased to 11%[333]

Among women, 9,342 were enrolled. The attendance was 65%. Among these, 1.3% had an AAA. After five years, three had died of AAA in the invited group and two in the control group[42].

As mentioned, in 1994, we started a randomised screening trial of 65-73 year old men in Viborg County [see above].

In 1996, 41,000 men aged 65-83 from the Perth area in Western Australia were identified by election lists and randomised[193]. The randomisation took place just after the identification, and the screening was not finished until 32 months later. Inclusion in the study started when the screening offer was mailed and the median date was chosen for the control group living in the same postage district. No strict standard for referral for surgery was given.

Records of causes of deaths were reviewed by an independent researcher blinded to knowledge of intervention group. The attendance rate was 63%. Among attenders, 7.2% had an AAA.

Follow-up ended in 2001. Overall, no statistical differences were noticed. However, a subgroup analysis of the most relevant group, i.e. men initially aged 65-74 on the date of screening, showed an odds ratio of 0.19 [95 % C.I.: 0.04-0.89] in favour of screening.

Based on the Chichester trial, a large multicentre trial [MASS] was initiated in 1997 randomising 67,800 65-74-year-old men in the areas of Portsmouth, Southampton, Winchester and Oxford. Inclusion ended in 1999. Men with an AAA sized above 55 mm, a growth rate above 1 cm annually, or a symptomatic AAA were considered for surgery. Cause of death was obtained from the Office of National Statistics and ICD codes for aortic aneurysms were used without revision. Consequently, some thoracic aneurysms must have been included. The attendance rate was 77%. Among attenders, 4.9% had an AAA. The mean follow-up time was 4.1 years when the researchers reported a mortality ratio of 0.58 [95% C.I.:0.42-0.78] in favour of screening[15].

Consequently, British and Australian Screening trials have been performed but a major question is whether the results can be generalised to other countries, as Scandinavia, due to different acceptability of the offer of screening, different prevalences of AAA, and different attitudes to surgery. In addition, hospital-based screening and AAA surveillance are much easier and more economically organized than screening at multiple general practitioners with 3-month surveillance of 45-54-mm AAAs.

In the UK MASS trial[15], the relative AAA-related mortality risk reduction was 42% [95% C.I.: 22% to 58%]. The difference not was significantly different from the 67% we observed. However, this contrast may be partly due to inclusion of unspecified aortic aneurysms, thoracoAAA and aortic dissections in the MASS trial, while the Viborg Study only included unruptured and ruptured AAA [ICD codes: I71.3 + I71.4].

The randomised trial in Western Australia[193] showed an insignificant relative risk of AAA-related death of 0.61 [95% C.I.: 0.33 to 1.11], but among the men aged 65-74, the relative risk was significant lower among the invited group [0.19, 95% C.I.: 0.04 to 0.89]. The findings from that study are thus consistent with the MASS trial and our findings that screening reduces mortality due to AAA.

As seen in figure 7, the cumulated prevalence of AAA-related death does not exceed 1 % in the control group, but a surprisingly 8% reduction in overall mortality was noticed – although not significant [P=0.052] – it leaves one wondering. However, apart from the Chichester Study, all three trials tended to reduce overall mortality. Significantly, in the Western Australian Study [Figure 10]. As mentioned earlier, information bias concerning AAA-related deaths will tend to underestimate the benefit gained by screening due to misclassification. In the MASS trial, the frequency of death due to AMI was actually significantly lower in the invited group[15]. Alternatively, the offer of screening may influence attenders life style positively.

Figure 10. Metaanalysis of the mid-term effects of screening 64-83 year old men for AAA concerning AAA-related mortality, total mortality and operations for AAA by indication.

In Figure 10, the midterm results [3-5 years] from the four randomised trial are pooled in a recent metaanalysis[334]. The analysis showed the offer of screening to men aged 65-80 years caused a significant reduction in AAA-related mortality of 53% [HR=0.47, 95% C.I.: 0.36;0.63]. In addition, a non-significant 3% reduction of overall mortality was seen. Nevertheless, the result is very interesting, as 3% overall mortality risk reduction is more than what could be expected by an approximately 50% AAA specific mortality risk reduction of a disease causing 2% of all deaths among men aged 65 or more [Figure 10].

A 3 times higher number of planned operations [P<0.05], and 45% fewer emergency operations were also noticed [P<0.05]. However, sign of heterogeneity was noticed concerning planned operations, probably due to a marked difference in the Western Australian Study compared to the European studies, This could be due to lack of an overall strategy for AAA repair, as the decision to refer patients for repair was given to the local doctors. Nevertheless, there seems to be quite robust data suggesting screening for AAA reduces AAA-related mortality and the frequency of emergency operations by increasing the number of planned operation on asymptomatic AAA-patients. Long term results will be interesting to see if these effects persist, and further studies must analyse whether screening is cost effective in Denmark and Western Australia.

5.1.2.2. Optimal interval screening and surveillance

It has been claimed that one single scan at the age of 65 is enough. However, the prevalence of AAA increases with age, and people live longer, also after development of other cardiovascular diseases. If screening programmes start at the age of 65, the men will at present live on average another 10-15 years. This seems sufficient to develop a clinically important AAA.

This opinion is supported by the above mentioned data from the MASS trial showing a rupture rate of 0.54 [95 C.I.: 0.25; 1.02] per 10,000 person years during seven years of follow up[335].

So re-screening may be needed, with unavoidable economic and psychological costs. The best solution would be to optimise selection for re-screening and to wait for as long as possible without jeopardising safety.

At re-screening after 3-5 years none of the 275 surviving and attending men with an initial normal aorta randomised to be offered re-screening had developed an AAA. Among those who initially had a 25-29 mm wide aorta, 28.5% had developed an AAA. It therefore seems possible that re-screening for AAAs can safely be restricted to attenders whose initial aorta width was 25-29 mm, and that it can be performed at five-year intervals. More recent and similar conclusions were made by the Gloucester and Huntingdon screening programmes among others [336-339], while the ADAM study [340] suggests a longer interval, and found that 2/3 of the interval cases would not have been detected if only cases with an initial diameter of 25 mm or more had been screened. However, their method for size measurement in normal cases is unknown, they used multiple observers, and strict standards are not reported.

Furthermore, surveillance of small AAAs also has psychological side effects[164;341], so control scans must be kept at a safe but minimal level. Initially, intervals were short [every 3-6 months], but by experience they have been prolonged. No consensus seems to exist at present. Based on the Gloucester and Viborg Studies, AAAs below 35 mm only need a rescan after three years, AAAs sized 35-39 mm in diameter need a rescan every second year, and AAAs sized 40-49 mm an annual rescan [299;337]. Gallard and Collin independently recommend rescan every 6 months in AAAs sized 40 mm or more[336;338;342]. The MASS trial uses rescan every 3 months if the AAA is 45-54 mm, and it will thus be possible to evaluate this strategy[15].

5.1.2.3. Ethical, psychological and stigmatising consequences

As mentioned in 1.7.2. Screening programmes risk causing fear. QoL among attenders is reported to be lower just before attending screening than after screening, which suggests some transient psychological stress, but changes are judged to be minor[164;165]. However, we found that screening for AAA probably requires only one scan in more than 90%. This must be taken into consideration when the observed transient reactions are evaluated.

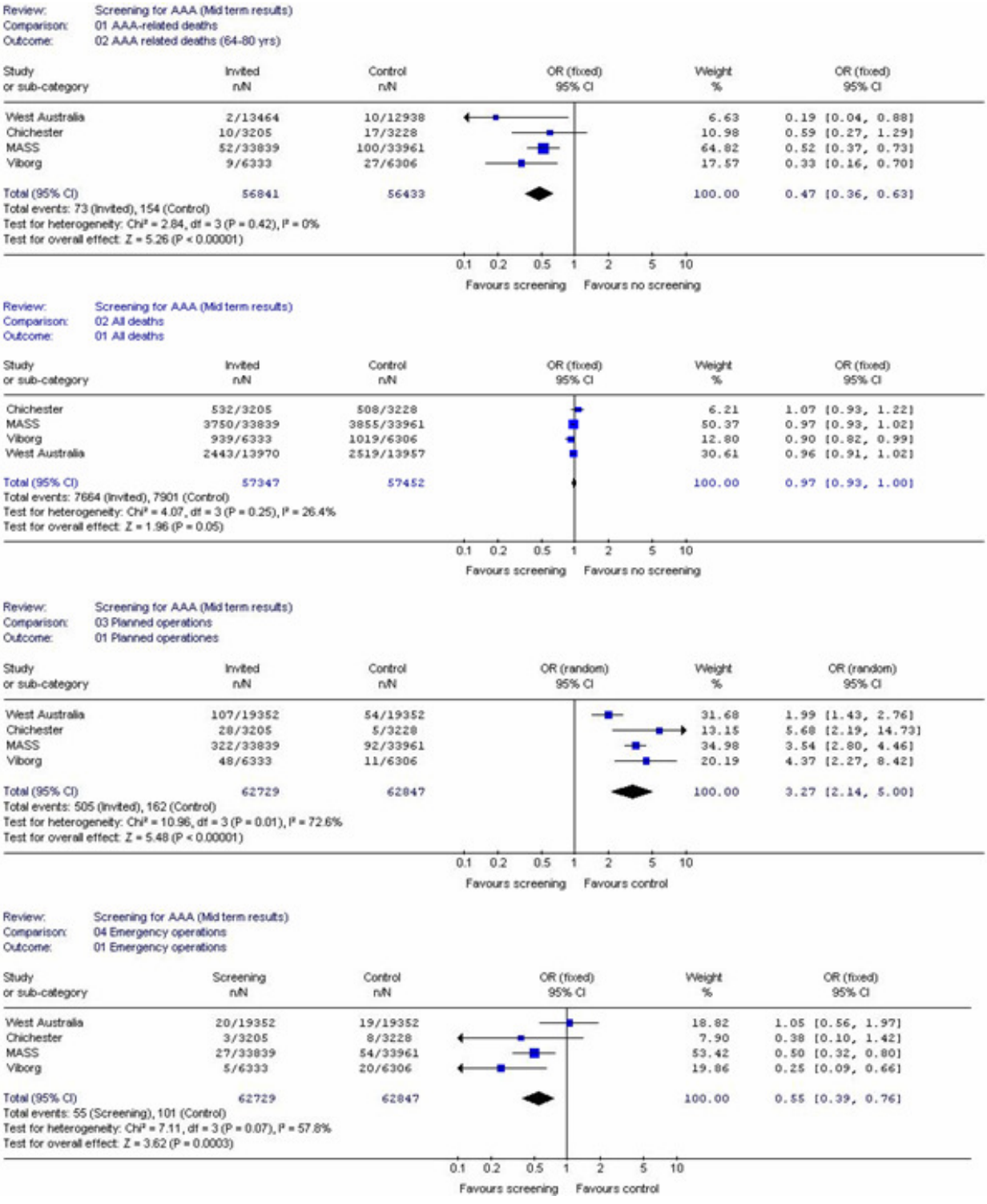


Figure 10. Metaanalysis of the mid-term effects of screening 64-83 year old men for AAA concerning AAA-related mortality, total mortality and operations for AAA by indication.

Prevalence by screening	N	Age					
		50-59	60-64	65-69	70-74	75-79	80+
Birmingham, UK(139)	2 669			8.4			
Gloucester, UK(152)¤	4 232			4.2			
Chichester, UK(64;344)	2 968			7.7			
Oldham, UK(345)¤	3 497			4.9			
ADAM, USA(41)	122 272			4.3			
Northumberland,UK(151)	628			6.9			
Liege, Belgium(343)¤¤	733			4.5			
Genoa, Italy(43)	741			8.8			
Oxford, UK(149;346)	426			5.4			
Huntingdon, UK(97)	3 030	2.3		8.8			11.9
Nijmegen, Holland(148)	2 419		8.1				
Gunma, Japan(347)	4 247		0.9				
Iverness, Scotland(150)	8 355			5.1			
South UK (MASS)(15)	27 147			4.9			
Western Australia	12 203			4.8	6.9	8.7	10.8
Viborg Study	4 852			4.0			

Table 11. Prevalence of AAA in mass screening studies. Prevalence per 100 screened. ¤: Only 65-year-old men. ¤¤:Only 65-and 70-year-old

5.1.2.4. Prevalence and incidences

The prevalence and incidence of AAA in older Danish men was unknown before the initiation of the screening program, and we found a prevalence of 4% among 64-73-year-old men, and by interval screening an incidence of 2.6/1000 observation years.

This prevalence is lower than in the similar studies from Chichester, MASS and Western Australia[147], but compares well to the findings in Malmö[45], Belgium[343] and the USA [41] [Table 11].

The incidence seems lower than in Huntingdon [UK], where it was 3.5 per 1000 observation years[339], but here the initial prevalence also seemed higher: 8.8% AAA among 65-79-year-old men[97].

We found an incidence of ruptured AAA in the control group of 1.07 per 1000 observation years; an incidence which in the Huntingdon Study in UK was found to be 0.73 per 1000 observation years but comparison is difficult due to different observation periods and a rising incidence[57].

In the control group, the incidence of AAA-related mortality was 1.04 per 1000 observation years.

Consequently, an increasing tendency seem present, as the mortality rate in 1991 varied from 0.42 per 1000 observation years among 65-69 year old men to 1.02 in men aged above 80 years old [Table 2].

5.1.2.5. Validity of the screening test

Allthough, it was not a major aim of the trial, the findings allowed us to do some estimations of the validity of the screening test because the exact sensitivity or specificity of US as a screening method is unknown.

By combining the SD of the interobserver variability with our observed size distribution of the infrarenal aorta [not shown], we estimated a diagnostic sensitivity of 98.9% and a diagnostic specificity of 99.9%[32]. We also found that problems with false positive and negative findings seem minor because they will be

High-risk group	Attended (n)	Frequency (Per cent)	AAA (n)	Prevalence (Per cent)	AAA-related deaths		AAA-related mortality rate in the control group per 1000 years
					Invited	Controls	
Hypertension	350	80.1 (76.6-84.3)	30	8.6 (5.9–12.0)**	2	5	2.15
AMI	528	82.5 (79.3-85.3)*	47	8.9 (6.6–11.7)**	0	7	2.03
COPD	328	71.8 (67.4-75.9)*	16	4.9 (2.8–7.8)	1	7	3.42
IHD excl. AMI	501	82.5 (79.3-85.5)*	35	7.0 (4.9–9.6)**	0	5	1.62
PAD	134	78.8 (71.9-84.7)	11	8.2 (4.2–14.2)	1	4	4.62
Stroke or TIA	215	73.1 (67.7-78.1)	11	5.1 (2.6–9.0)	1	4	2.34
All at high risk	1324	78.8 (76.7-80.7)*	88	6.7 (5.4–8.1)**	4	18	1.99
All at low risk	3528	75.8 (74.6-77.1)	103	2.9 (2.4–3.5)	5	21	0.74
All	4852	76.6 (75.6-77.7)	191 -	4.0 (3.4–4.5)	9	39	1.05

Table 12. Attendance rates to screening, prevalence of AAA and AAA-related deaths in six groups at high–and at low risk for AAA [95% confidence intervals in parentheses]

***: P-value <0.05 for the proportion of attenders to screening in the specific high-risk group compared with those not included in the specific high-risk group as reference.**
****: P-value of the proportion of having an AAA for men in the specific high-risk group using those not included in the specific high-risk group as reference.**

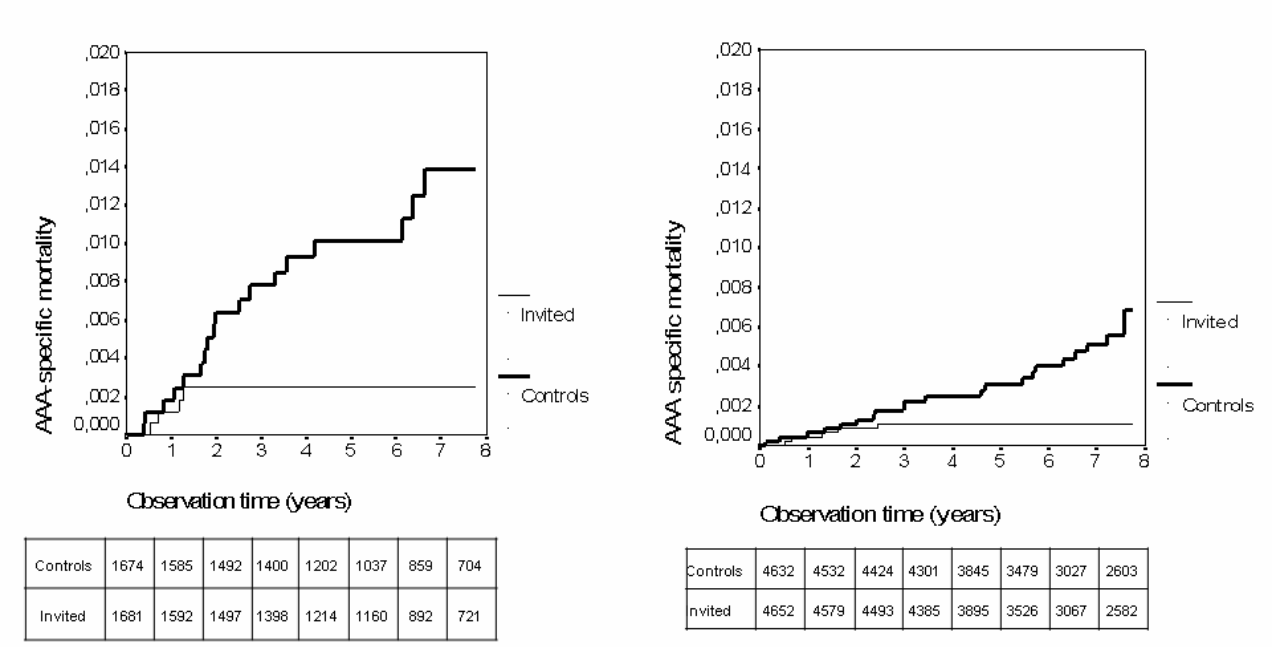
revealed by surveillance of small AAAs and interval screening of pre-aneurysmal dilatations.

Two false positives out of 238 positive findings [1%] were found at the following control scan, no negative findings have later been operated for AAA, and no cases diagnosed by interval screening were recommendable for surgery at the diagnosis. There are apparently no comparable reports, but in the large Huntingdon screening programme Wilmink et al. tried to identify false negative tests by tracing all patients with a ruptured aneurysm or operated later. False positive tests were identified as aneurysmal aortas by US that were classified as normal by CT. They found no false negative or false positive findings[146]. However, the Huntingdon screening programme have offered rescreening to men with preaneurysmal dilatations[339]. This is not offered in the large multicentre screening study, MASS trial. Recently, they reported after a mean follow up of seven years a rupture rate of 0.054 [95 C.I.: 0.25; 1.02] per 1000 observation years among attenders with a normal aorta at screening[335].

The aorta cannot be visualised in 0-2.5%[32;63;137;152;348].We have previously found that the distal part of the infrarenal aorta could be visualised in 99.7% and the entire infrarenal aorta in 98.5%.The visualisation rate of the distal part of the aorta has largely remained unchanged , but that of the entire infrarenal aorta rose from 98.3% in 1994 to 99% in 1996[32]. In all, there seems to be a valid screening method present.

5.1.2.6. Feasibility of screening of 64-73 year old men in Denmark

The attendance proportion of those invited to screening and mid term results show indirectly that hospital based screening of 64-73 year old men in Denmark is feasible. It was possible for the local organisatory and administrative system to identify the target group, the mobile screening team to manage dataregistration, reinvitations and recalls for AAA surveillance, secure the treatment capacity at the start of the programme [The prevalence screening phase], inform the participants, coordinate further visitation and continue to be sufficiently educated.



Controls	1674	1585	1492	1400	1202	1037	859	704
Invited	1681	1592	1497	1398	1214	1160	892	721

Controls	4632	4532	4424	4301	3845	3479	3027	2603
Invited	4652	4579	4493	4385	3895	3526	3067	2582

Figure 11+12. Kaplan-Meier estimates of mortality from AAA. Screening group and control group among men with [1st figure] and without [2nd figure] known COPD and/or cardiovascular disease

5.2. STRATIFIED ANALYSIS IN THE RANDOMISED POPULATION SCREENING TRIAL FOR AAA IN MEN, WITH OR WITHOUT HOSPITAL DIAGNOSES OF COPD OR CARDIOVASCULAR DISEASE, IN ORDER TO EVALUATE WHETHER THE OFFER OF SCREENING IS ACCEPTABLE TO THOSE AT HIGH RISK OF HAVING AND AAA, AND TO EVALUATE WHETHER THE OFFER OF SCREENING MAY BE RESTRICTED TO SUCH MEN IN HIGH RISK [STUDY II].

5.2.1. Major findings

We found that the attendance proportion of invited men to screening for those men previously admitted to hospital due to COPD or cardiovascular diseases, including hypertension, was 78.8% [76.7-80.7%] compared to 75.8% [74.6-77.1%] for men without such previous hospital admissions [P<0.01] [Table 12]. If only the high risk group was invited to screening for AAA, only 27% of the male population study would have been in target group for screening but we would only have diagnosed 46.1% of the AAA cases diagnosed by mass screening. The prevalence of AAA was 6.7% compared with 2.9% among the men without such previous hospitalizations [P<0.001]. Highest in the subgroup of patients previously submitted due to AMI [8.9% [95% C.I.: 6.6-11.7%]].

In all, 22 died due to AAA in the high risk group: 4 in the invited group and 18 in the control group [hazard ratio: 0.22 [95% C.I.: 0.08-0.65], P = 0.006, Figure 11].

Overall, 39 died of AAA in the control group and 9 in the invited group. Consequently, high risk screening alone would have prevented 14 of the prevented 30 AAA related deaths observed in the population screening trial, corresponding to 46.7% [95% C.I.: 28.3-65.7%]. In the low risk group, 26 subjects died of AAA-related causes: 5 from the invited group and 21 from the control group [hazard ratio: 0.24 [95% C.I: 0.09-0.63, P= 0.004, Fig. 12].

Figure 11+12. Kaplan-Meier estimates of mortality from AAA. Screening group and control group among men with [1st figure] and without [2nd figure] known COPD and/or cardiovascular disease

5.2.2. Discussion of the major findings in study II

5.2.2.1. An acceptable screening method?

The Council of Europe emphases that an acceptable screening method requires a sufficient attendence proportion to screening for high risk groups. Low age, high social class, marital status and short travel distance to the examination facility are reported to be independent predictors of participation. Season of the year and diseases influencing mobility apart from cardiovascular disease and COPD do not influence attendance[63;150;153;349]. Age, social deprivation, cardiovascular disease, COPD and secondary recruitment [revised appointment or re-invitation] are reported to be independent risk factors of AAA, while marital status and travel distance did not predict AAA[63;150;153;349].

The present work confirms a small but unique positive selection to screening concerning AAA-associated diseases. Age selection and social deprivation are unfavourable since the attendance rate decreased with age and social deprivation, while the risk of AAA increased. However, the age selection

will disappear in continuous screening programmes starting at the age of 65 years.

However, such considerations seem not sufficient concerning AAA screening since those in high risk of having an AAA are especially patients with cardiovascular manifestations, so the treatment may become unacceptable. This could leave a large proportion of untreated men at high risk of aneurysm rupture and those offered operation could have increased risk of postoperative complications and deaths. In all, the benefit of screening of a high risk group could be limited or in the worst case scenario even harmfull. This seems not to be the case, as screening decreased AAA related mortality equally among men with and without AAA-associated diseases [78 and 76%, respectively. So, the offer of screening to men in the high risk group seems acceptable based upon attendance rate and benefit of screening. There seems not to be any comparable reports.

5.2.2.2. Can screening for AAA be restricted to men in high risk due to cardiovascular and pulmonary comorbidity?

Whether it should be limited to this group is more doubtful, since screening decreased AAA related mortality equally among men with and without AAA-associated diseases [78 and 76%, respectively]. The absolute risk reduction was approximately twice as high in the high risk group with 95 numbers needed to screen in order to prevent one death compared to 220 in the low risk group. However, 220 needed to screen to save one life is also quite low, and the diagnostic costs of detecting an AAA in the group of men without AAA-associated disease was only approx. £150 higher than in the high risk group[16]. This is a small difference, and it must be kept in mind that direct screening costs count less than 5-10% of the total screening costs in the Viborg Study[350]. Moreover, the overall mortality is logically significantly higher among men with AAA with AAA-associated diseases than in men without AAA with coexististing AAA-associated diseases adjusted for age [mortality ratio: 1.76 [1.18-2.60], P=0.005] [Figure 13, unpublished data].

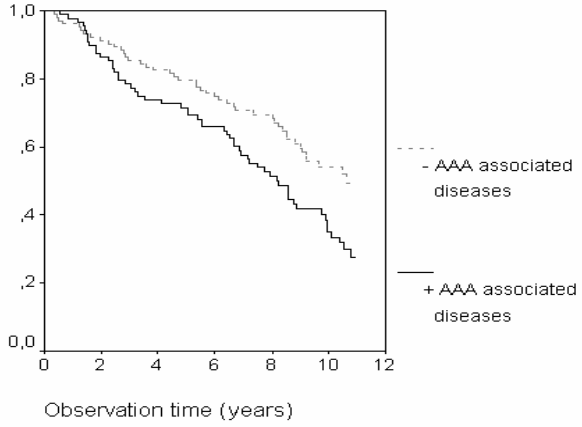


Figure 13. Survival of men with screen-detected AAA with and without AAA-associated diseases in the Viborg Study [unpublished data]

Consequently, the number of saved living years per saved life in the low-risk group must be higher than in the high-risk group.

Alternatively, more men could probably have been included in the high-risk group, if we had searched the written hospital and GP records but this is hardly worth the effort, since mass screening only takes below 10 minutes including invitation, information, scanning and registration. Nevertheless, low risk screening seem justified based upon the interpretation of these results, but a final and firm conclusion can only be based upon a long term effectiveness analysis, as performed later in study III.

Considerations of whether the offer of screening for AAA can be limited to specific high risk groups have also been addressed concerning smoking and a family history of AAA. The large ADAM study focused on smokers and found that 90% of the screen-detected AAAs were found in current or former smokers, who made up 70% of the screened population[212;351]. Consequently, the US Preventive Task Force recommended screening but only men who currently or once smoked. They also examined the potential role of selective screening of siblings and noted that only 5.1% of the men with a screen-detected AAA had a family history of AAA[212]. These large-scale American findings are similar to our findings in the Viborg Study, where only 3.3% of the men having an AAA told that they had never smoked compared with 18% in en random sample of attenders without an AAA[16]. Furthermore, only 6% had a family history of AAA – which was similar to the ADAM study. Others have reported that up to 20% of AAA patients have a family history of AAA, but these data are not based upon population screening data, and could be biased by a local interest in family AAA with increased opportunistic screening of siblings as a consequence. Restricting screening to silings of AAA patients would, however, hardly be sufficient to achieve a substantial reduction in the mortality of AAA compared with mass screening[16].

5.2.2.3. Risk factors for AAA

Finally, numerous screening studies on more or less selected patient groups have assessed risk factors for AAA, some of which are listed in Table 13. The most constantly mentioned risk factors are age, male sex, hypertension, IHD, COPD and arteriosclerosis of the carotid or lower limb arteries[43;139;206-218]. In a recent Brazilian study, coronary CT-angiography was done in synchronously with the CT-scanning of the aorta. It revealed that 76% had coronary atherosclerosis, and 20% had at least one lesion more than 70%[352].

Strangely, diabetes mellitus – a consistent risk factor of atherosclerosis – has been associated with decreased risk of AAA[209;210;353]

The present study [II] allowed a population based study of the associated risk of AAA in patients with existing comorbidity.

High-risk-group	Selection	AAA	Ref
Relatives of people with AAA	Brothers	0.17	1*
	Sons	0.27	1*
	Brothers	0.29	2*
	Sons	0.21	3*
	Daughters	0.03	3*
	Female siblings	0.16	4*
	Male siblings	0.43	4*
	Brothers	0.29	5*
	Sisters	0.11	5*
	Male 1st degree	0.11	6
	Female 1st degree	0.00	6
Abdominal ultrasonographic scan indicated	Men above 60 years	0.11	7
Abdominal CT-scanning indicated	Men above 50 years	0.14	8
Urological patients	None	0.10	9
History of inguinal hernia repair	Men above 55 years	0.12	10
Patients for echocardiography	None	0.00	11
Cardiologic patients	Men above 60 years	0.11	12
Patients for echocardiography	Above 50 years	0.05	13
Patients for cardiac catherization	None	0.08	14
Cardiology clinic patients	Male above 55 years	0.04	15
Severe IHD	Male above 55 years	0.07	15
Smokers (autopsy-study)	None	0.11	16
COPD	None	0.10	17
COPD	Men 65-73 years	0.05	(II)
Previous AMI	Men 65-73 years	0.09	(II)
Ishaemic heart disease excl. AMI	Men 65-73 years	0.07	(II)
Hypertension or coronary atherosclerosis	None	0.09	18
Coronary atherosclerosis	Above 60 years	0.14	19
Patients for coronary bypass	Men above 60 years	0.10	20
Patients after coronary bypass	Men above 50 years	0.11	21
Hypertension	Men 65-73 years	0.09	(II)
Hypertension	Men above 50 years	0.20	22
Hypertension	None	0.20	23
Hypertension	None	0.07	24
Hypertension	None	0.14	25
Hypertension or coronary atherosclerosis	None	0.09	18
Intermittent claudication	None	0.15*	26
Peripheral vascular disease	None	0.14	27
Peripheral vascular disease	None	0.10	28
Peripheral vascular disease	None	0.10	29
Peripheral vascular disease	Men	0.11	30
Peripheral vascular disease	Women	0.06	30
Lower limb atherosclerosis	Men 65-73 years	0.08	(II)
Carotid artery evaluation	None	0.08	31
> 50% carotid stenosis	None	0.18	32
< 50% carotid stenosis	None	0.12	32
Stenosis of carotid artery	None	0.11	31
Normal carotid artery	None	0.07	31
Previous stroke or TCI	Men 65-73 years	0.05	(II)
Familial hypercholesterolemia	Men	0.33	33

Table 13. Risk factors for AAA. Cross sectional screening studies.

We found AAAs in 8.6% [5.9-12.0%] of men with hospital-diagnosed hypertension, 8.9% [6.6-11.7%] with previous AMI, 7.0% [4.9-9.6%] in cases with IHD excluding AMI, 4.9% [2.8-7.8%] in cases with COPD, 8.2% [4.2-14.2%] in cases with lower limb atherosclerosis and 5.1% [2.6-9.0%] in cases with previous stroke or TIA [Table 6]. Furthermore, the risk is increased by smoking[209;212;348;351;354-358], and alcohol consumption [43;359].

A gigantic population screening study in the USA involving 73,451 veterans found that smoking was the risk factor most strongly associated with AAA; the OR for AAAs of 4.0 cm or larger compared with normal aortas was 5.57. The association between smoking and AAA increased significantly with the number of years of smoking and decreased significantly with the number of years after quitting smoking. The excess prevalence associated with smoking accounted for 78% of all AAAs that were 4.0 cm or larger in the study sample.

Female sex [OR: 0.22], black race [OR: 0.49] and presence of diabetes [OR: 0.54] were negatively associated with AAA. A family history of AAA was positively associated with AAA [OR: 1.95], but was only reported by 5.1% of the participants. Other independently associated factors included age, height, coronary artery disease, any atherosclerosis, high cholesterol levels and hypertension[212].

A recent systematic review of population-based screening studies discovered 14 relevant cross-sectional studies. Most studies screened people aged 60 years or older. The prevalence of AAA ranged from 4.1% to 14.2% in men and from 0.35% to 6.2% in women. Male sex was strongly associated with AAA [OR: 5.69], whereas smoking [OR: 2.41], a history of AMI [OR 2.28] or peripheral vascular disease [OR: 2.50] showed more moderate associations. Hypertension was only weakly associated with AAA [OR:1.33] and no association was evident with diabetes [OR: 1.02][209].

The large prospective Malmo Preventive Study followed 22,444 men and 10,982 women for a median follow-up of 21 years; 126 men developed large AAAs above 5 > or had autopsy-verified ruptured AAAs. The men developing a large AAA later had increased diastolic blood pressure [p<0.001] at the initial health screening, smoked more frequently [p<0.0001] and were more often physically inactive. No difference in forced vital capacity or BMI was seen. Among the laboratory markers measured, the erythrocyte sedimentation rate did not differ but total cholesterol [6.3+/-1.12 vs. 5.8+/-1.0] [p<0.0001], triglycerides [1.9+/-0.12 vs. 1.5+/-0.07] [p<0.001] and the inflammatory proteins: alfa-1-antitrypsin, ceruloplasmin, orosmucoid, fibrinogen, and haptoglobulin, were significantly increased in men later developing AAAs[360] .

Finally, the risk is probably increased by genetic transmission, because first-degree relatives of persons with AAAs have up to 10 times higher risk of AAA, mostly a 2-4 times higher risk[28;361;363-365;386-395].

In the Western Australian Screening Trial, the prevalence of AAA was higher than average in men originating from The Netherlands or Scotland and lower in men of Mediterranean origin, but no association with dietary habits was found [396].

The prevalence of AAA in a Japanese study was only 0.9% in 65-74-year-old men[347], and thus contrasts the other screening studies in table 4. In other words, indications of genetic causes are indeed present.

Several studies have attempted to find the candidate gene for AAA. For instance, we have previously reported that the apolipoprotein E genotype was associated with the expansion rate of the AAA[397], while others have demonstrated an increased frequency of a 4G/5G mutation in the plasminogen activator inhibitor-1 [PAI-1] gene in familial cases of AAA[277].

However, many of the genes for the proteases and cytokines involved in the AAA pathogenesis have polymorphic sites which may in part explain the genetic predisposition of some individuals. Using segregation analysis, Verloes et al, concluded that an autosomal dominant gene with an allel frequency of 1:250 and 40% penetrans would be the most likely genetic cause of AAA[393]. A large multinational study of 233 families with 2 or more cases of AAA concluded that the assumed genetic causes would be autosomal recessive in 72%, autosomal dominant in 25% and the rest to be autosomal dominant with incomplete penetration[398]. Several genetic models were compared by Majumder et al, who found AAA more likely to be caused by a recessive gene at an autosomal major locus[389].

The disagreement can be taken as no simple genetic explanation can exist. Although significant associations have been found between certain gene polymorphisms and AAA [see part 2.2 for specific findings], it seems not realistic that one single gene will show up to be a critical factor. A genetic caused down regulation of any particular cytokine, protease or pathway will probably be counterbalanced by up-regulation of compensatory pathways. It seems more realistic, that particular combinations of polymorphisms predispose to AAA formation, but any individual gene will have a limited effect. Whole genome studies seem needed to understand the genetic predisposition of AAA. However, no pure genetic explanation seems realistic. The association to male sex, smoking, alcohol consumption and physical activity suggests environmental causes also are involved.

5.2.2.4. Potential prescreening alogoritme for AAA in Denmark.

Study II focused on the hypothesis that it would be possible to prescreen for identifying those having most risk of AAA. This could also be done by a questionnaire send by the general practioner asking about other risk factors as lifestyle including smoking, familiar tendency til AAA and perhaps hypertension, pulmonary and cardiovascular disease. This would of course need some administrative work and additional costs for postage, which must be balanced to screening itself only takes 5 minutes, and it would not reduce the

number in risk so much. The US TASK FORCE recommends screening of men aged 65 if they have ever smoked. In the ADAM study, 80% of the relevant men did smoke or had smoked, and 90% of those having an AAA diagnosed smoked or had smoked. Consequently, this could be a way to reduce the numbers offered screening, but apparently not much and the quality of the memory based data could be debated. The national screening programme in UK being implemented these years, do not differentiate due to this factor.

If a first degree sibling of yours has an AAA, your own risk of having one increases 3-5 times, but such family disposed cases only count for about 5% of the AAA detected by mass screening. Cardiovascular disease are coexisting diseases which approximately doubles the risk of AAA, it is not associated with faster expansion - rather the contrary, but is associated with higher morbidity, lower quality of life and lower expected survival and, as shown in study II, it detects only half of the cases detected by mass screening. Actually, the results from study III indicate that it is not as efficient to reduce relative AAA-specific mortality on the long term basis, while the cost effectiveness analysis of that subgroup analysis is uncertain, while offering screening to those in low risk is cost effective.

Eighty percent of all ruptured AAA happens in men aged 65 or more. General population based screening of men aged 65+ have proven effective in UK, Denmark[I,II,III] and Western Australia. In addition, it is proven on evidence 1B level to be cost effective in UK, and very cost effective in Denmark [III]. Conseqeuently, it seems difficult to argue against even more selection to screening for those in that age group and with that gender. Howerever, still ruptures happens in younger men, but seldom below 60, and in women. Selected screening of younger men and women could therefore beneficial. In table 14, a suggestion for a Danish screening alogoritme has been summarised. One could imagine that additional selective screening offers ought to be offered to men aged 60-64 and women above 60, if they has a family history of AAA, cardiovascular manifestations or hypertension. Preaneurysmal dilatations could then be rescreened in five year intervals, although the oprtimal interval is not known. A large englisk HTA is ongoing with representatives from the four randomised screening trials among others in orther to answer that question. Finally, it must be emphasised, that such an algorithm has vener been tested, but it pure theorectical [Table 14].

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Conseqeuently, it seems difficult to argue against even more selection to screening for those in that age group and with that gender. Howerever, still ruptures happens in younger men, but seldom below 60, and in women.

Table 14. Potential alogoritme for Danish persons to be offered screening for AAA

Men	
Aged 60-64:	Family history of AAA Hypertensio arterialis Previous transient cerebral Ischemia or stroke Ischaemic heart diseace +/- previous acute myocardial infarction Lower limb ischaemia
Aged 65	All
Aged 70-75	*Five year interval screening of men with an aortic diameter 25-29 mm*
Woman	
Aged 65+	Family history of aneurismal disease Hypertensio arterialis Previous transient cerebral ischemia or stroke Ischaemic heart diseace +/- previous acute myocardial infarction Lower limb ischaemia
Aged 70-75	*Five year interval screening of women with an aortic diameter 25-29 mm*
Consequences of the scanning:	
AAA diameter 30-39 mm:*	*Ultrasound surveillance after 2 years*
AAA diameter 40-49 mm:*	*Ultrasound surveillance after 1 year*
AAA diameter 50 mm+:*	*Referrel for CT skcanning and potential surgery*

*: Initiation of general cardiovascular preventive actions as lifestyle modification, smoking cessation motivation, antiplatelet treatment, statins, and proper antihypertensive treament

Selected screening of younger men and women could therefore beneficial. In table 14, a suggestion for a Danish screening alogoritme has been summarised. One could imagine that additional selective screening offers ought to be offered to men aged 60-64 and women above 60, if they has a family history of AAA, cardiovascular manifestations or hypertension. Preaneurysmal dilatations could then be rescreened in five year intervals, although the oprtimal interval is not known. A large englisk HTA is ongoing with representatives from the four randomised screening trials among others in orther to answer that question. Finally, it must be emphasised, that such an algorithm has vener been tested, but it pure theorectical [Table 14].

5.3. BENEFIT AND COST EFFECTIVENESS ANALYSIS OF SCREENING FOR AAA BASED ON 14 YEARS RESULTS FROM A SINGLE-CENTRE RANDOMISED CONTROLLED TRIAL [STUDY III].

5.3.1. Major findings in study III

5.3.1.1. Benefits of screening for AAA

The hazard ratio for AAA related mortality during the 14 years observation period between those offered screening and those not offered screening was estimated at 0.34 [95% C.I.: 0.20;0.57], p<0.01 [Figure 14] – for men aged 65: 0.36 [95% C.I.: 0.14;0.93], those in high risk of having an AAA: 0.42 [95% C.I.: 0.20;0.87], and those in low risk of having an AAA: 0.29 [95% C.I.: 0.14;0.57].

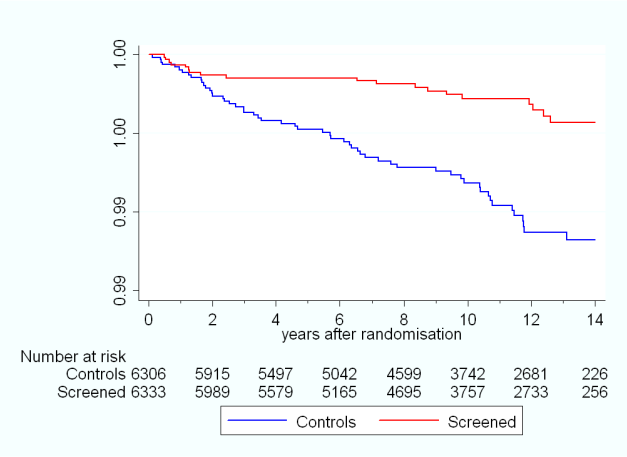


Figure 14. Survival curves from AAA related mortality after being offered screening for AAA or not [Study III]

The hazard rate for all cause mortality was reduced for the screening group but not statistically significant even with adjustment for age and known hospital treated disease at baseline [HR: 0.98 [95% C.I.: 0.93;1.03] [Figure 15].

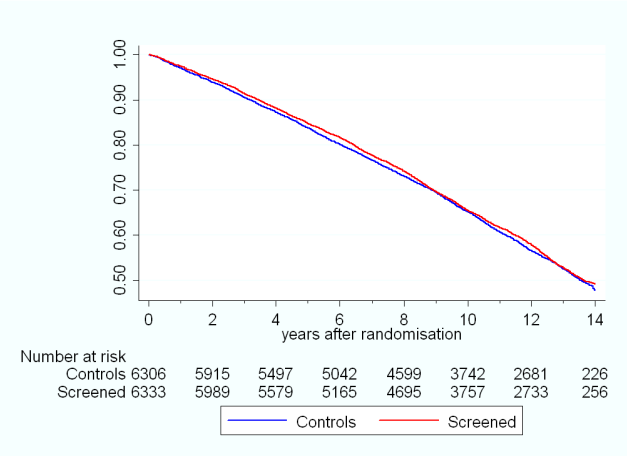


Figure 15. Survival curves from all cause death among men invited to screening or being controls.

During the 14 years observation period the sample experienced 133 planned AAA operations, 12 AAA operations without rupture and 52 operations with rupture. The 30 days postoperative mortality after EAAA, AAAA and RAAA, 3.0% [95% C.I.: 0.1;7.1%], 33.2% [95% C.I.: 11.6;62.3%] and 57.7% [95% C.I.: 44.0;70.5%], respectively.

The hazard rate for a planned AAA operation was estimated at 2.00 [95% CI: 1.40;2.88] for the screening group, while the hazard rate for acute AAA operations without and with rupture was estimated at 0.50 [95% CI 0.15;1.65] and 0.44 [95% CI 0.25;0.81].

5.3.1.2. Cost effectiveness of screening for AAA

The cost per life year gained could be calculated at 157€ [1,170 DKK] [95% CI -3,292;4,401] and the cost per QALY at 178€ [1,326 DKK] [95% CI -4,083;4,682] [Table 15].

	Control group (n=6,306)	Intervention group (n=6,333)
Life years	9.99 (9.89;10.09)	10.08 (9.98;10.18)
Life years, discounted 3%	8.46 (8.38;8.54)	8.54 (8.46;8.62)
QALYs	8.52 (8.44;8.61)	8.60 (8.52;8.69)
QALYs, discounted 3%	7.24 (7.17;7.30)	7.31 (7.24;7.37)
Cost	315 (245;384)	332 (272;392)
Cost, discounted 3%	298 (231;366)	311 (255;366)
of which		
- invitations	-	3 (3;3)
-screening	-	19 (18;19)
-control scanning	-	9 (7;10)
-elective surgery	90 (64;117)	193 (153;233)
-acute surgery without rupture	33 (10;55)	14 (0;28)
-acute surgery with rupture	176 (118;233)	73 (37;109)
Cost per life year gained		157 (-3,292;4,401)
Cost per QALY gained		178 (-4,083;4,682)

Table 15. Estimation of costs per life year and quality adjusted life year [QALY]. Values are means [95% confidence intervals]. All costs are in 2007-€

5.3.1.2. 1. Sensitivity analyses of cost effectiveness of screening for AAA

The analysis of the subgroup aged <=65 years was conducted in 5,429 men and demonstrated a potentially increased ICER to 1,308€ [9,745 DKK] [95% CI -10,895;13,581] in the subgroup. This increase was due to a minor increase in the average incremental cost of providing the screening programme - from €12 to €91 - while the mortality benefit was reduced from, on average, 0.08 life years to, on average, 0.07 life years [Figure 16].

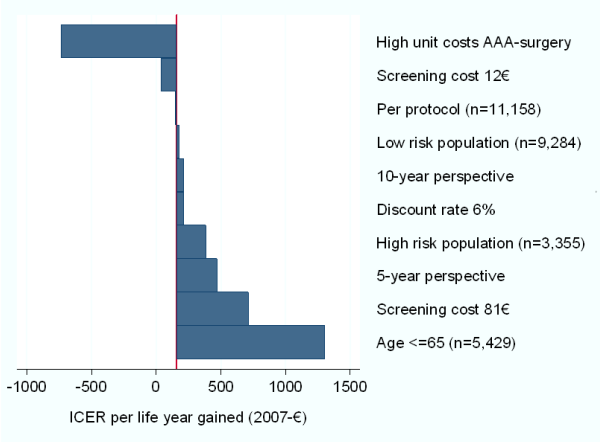
The subgroup analysis in high-risk men only [n=3,355] suggested, in contrast to a 58% reduction in AAA-related mortality, screening to be associated with a negative benefit of, on average, -0.04 life years but at a cost saving of 14€, which altogether yielded an ICER estimate of 385€ [2,868 DKK] saved per life year less gained [95% CI -9,373;10,051]. It should be noted that given the relatively modest sample size in the subgroup analysis the precision of this finding is far from optimal beyond a purpose of generating hypotheses. The corresponding figures for the subgroup of low-risk men [n=9,284], as compared to base-case, were an increase in the average incremental costs to 22€, an increased average gain in life years to 0.11, and an ICER estimate of 182€ [1,356 DKK] [95% CI -1,377;2,208].

Using higher unit costs for acute AAA surgeries by including the mentioned outliers in estimation of the actual costs [increasing the cost of surgery without rupture from 27,628€ to 34,858€ and the cost of surgery with rupture from 35,928€ to 58,536€] lowered the ICER per life year gained to -734€ [5,468 DKK] [95% CI -8,496;6,630]

Another potential alternative scenario concerns the item cost estimate for ultrasonography; using the HRG tariff [81€ per screened] and thus assuming that no economies of scale exist for a permanent routine program [in the hospital-based setting] lead to an ICER of 715€ [5,328 DKK] per life year gained [95% CI - 4,896;8,083].

The impact of alternative specifications of key parameters is presented in Figure 16.

Figure 16 Impact on the incremental cost-effectiveness ratio [ICER] of alternative parameter specifications. Bars represent deviations from base-case at an average of ICER=157€ per life year gained.



Note: Sensitivity analyses were conducted in the full sample of N=12,639 unless otherwise specified. AAA = AAA. High unit costs AAA-surgery refer to those reported by Lindholt and Sorensen[304]. High-risk population refers to the subgroup with known AAA-related comorbidity and vice versa for the low-risk population.

5.3.2. Discussion of the major findings in study III

In 2005, a systematic review and meta-analysis was made by the American preventive task force[399]. It identified 4 population-based randomized, controlled trials of AAA screening in men 65 years of age and older and calculated that the offer of screening significantly reduced AAA-related mortality with an odds ratio of 0.57 [95% C.I.: 0.45; 0.74]. Shortly hereafter, the American Preventive Task Force, working for the American government, recommended screening 65-year-old men who currently or ever smoked.

In the spring of 2006, the UK National Screening Committee followed the American Preventive Task Force and recommended screening of all 65-year-old men for AAA. Consequently, several regions and countries are now considering introducing AAA screening. However, the Chichester Aneurysms Screening Trial reported poor long-term benefit [see above]. We therefore supplemented the previously published data with a long term benefit and cost effectiveness analysis after fourteen years of follow up.

5.3.2.1 Benefits of screening

The Viborg Study thus holds no overall signs of an impaired long-term benefit. Recently, the Huntingdon screening study published their non-randomised results: after five years the reduction in the incidence of RAAA was 49% [95% CI: 3-74%]. After 13 years of screening the incidence of RAAA was reduced by 73% [95% CI: 58-82%], and screening had reduced the mortality from RAAA by 75% [95% CI: 58-84%][400].

In Maj 2007, MASS trial reported their seven year results; The hazard ratio was 0.53 [95% CI, 0.42 to 0.68] for AAA-related mortality in the group invited for screening[335], and now suggest that the inclusion of deaths from aortic aneurysm at any site, may have included some thoracic aortic aneurysms, so the screening effect may be underestimated. In June 2009, MASS trial reported their ten year results; as well the hazard ratio for AAA-related surgery was unchangded 0.52 [95% confidence interval 0.43 to 0.63], as well as the hazard ratio for overall mortality [0.97, 95% C.I.: 0.95 to 1.00] [335].

These results support our results that a long-term benefit is, indeed, possible, but they also emphasise the need for an optimal surveillance because the number of men with small AAA lost for follow up, was a major reason for the poor long-term benefit according to the Chichester group.

After the finding of a tendency of reduced overall mortality in the Viborg Study after 4-5 years [I], an interesting question was whether this tendency would continue. After 14 years, the overall mortality was reduced by 2%, and this was not significant [III]. However, the sample size was never powered sufficiently to be able to detect such small differences. In MASS trial, the observed hazard ratio concerning all cause mortality was 0.97 [CI, 0.95 to 1.00] at the 10-year follow-up study. This was very close to be significant. In figure 16, a metaanalysis of the updated results from the four randomised trials is presented. There are still no long term results concerning AAA related deaths from the Western Australian Screening study, so their they are left out for this long term analysis.

The analyses of the long term results showed the offer of screening caused a significant reduction in AAA-related mortality of 45%. An insignificant 2 % reduction of overall mortality was also noticed [0.98, 95% C.I.: 0.96;1.00] based upon the seven year results from Viborg. However, in an earlier metaanalysis using the seven year results fra MASS and study II, the overall mortality was significantly reduced by 3% [OR=0.97, 95% C.I.: 0.94 to 0.99]. For interpretation, one has to remember the effect of screening and the data used in the calculation of odds ratios. The benefit of screening is a delay of death but in the end, we are all going to die.

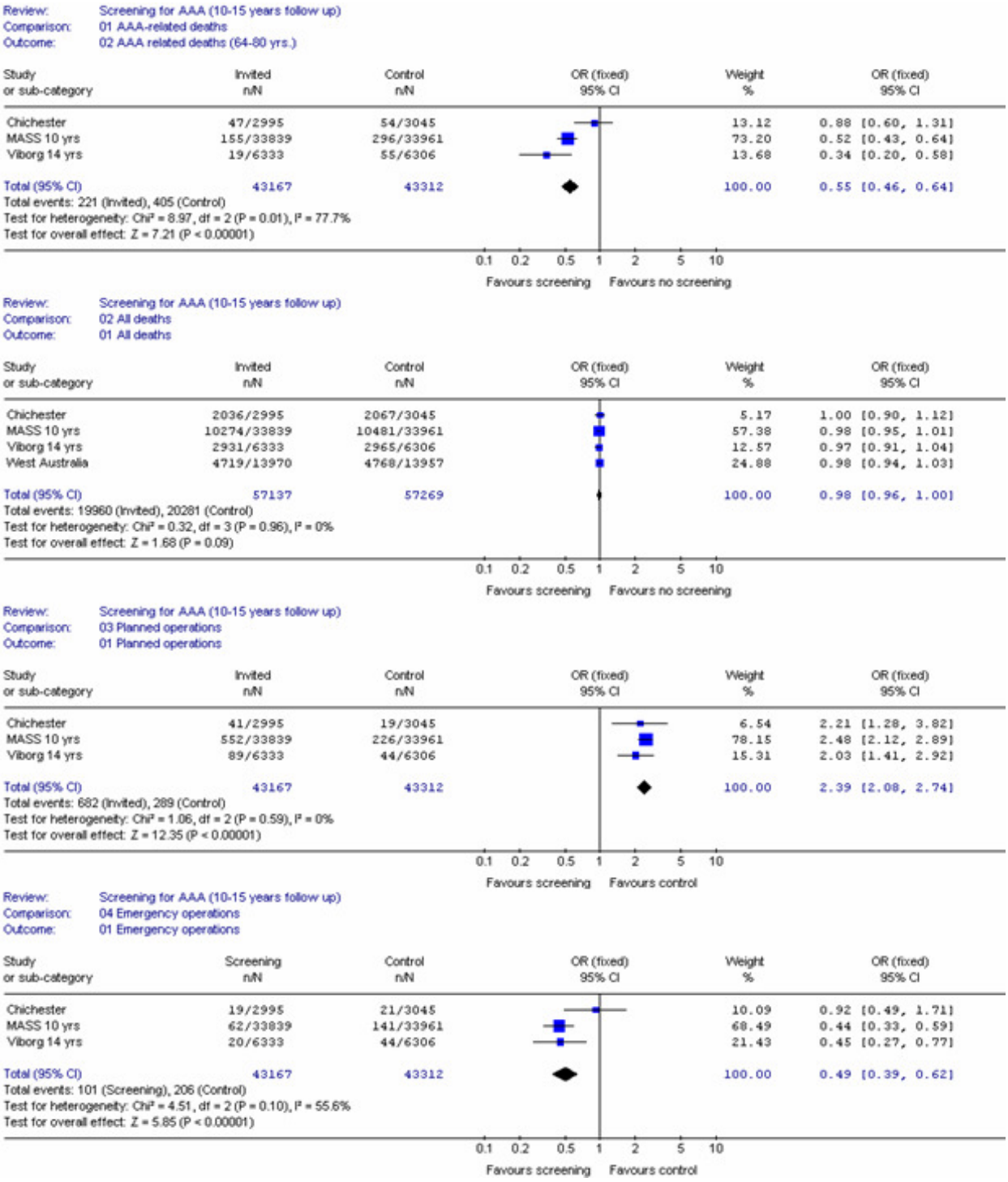


Figure 17. Metaanalysis of the long-term effects of screening 64-83 year old men for AAA concerning AAA-related mortality, total mortality and operations for AAA by indication[334].

A significant 2.4 times higher number of planned operations, and 51% fewer emergency operations was also noticed. [Figure 17]. In all, there was 1.6 times more operations in the invited group compared to the controls [OR=1.59, 95% C.I.:1.42;1.78]. Consequently, there is quite robust data suggesting screening for AAA reduces AAA-related mortality, overall mortalty, the frequency of emergency operations by increasing the number of planned operation on asymptomatic AAA-patients, also on the long term basis. It seems realistic that screening for AAA provides substantially more benefit, than the benefit obtained by reducing AAA-mortality. The collaboration between the randomised trials [The CASS collaboration] could produce a robust analysis on that topic[147], but initialized collaboration has still not been completed.

5.3.2.1.1. Benefits of screening 65 year old men

All randomised trial recruited participants older than 65 years who are expected to be offered screening in permanent programmes. Older age increases the prevalence of AAA but decreases the attendance rate, and whether the results can be generalised to 65 year old men are unknown. The Viborg study recruited over 5 year's consequtively new generations of 65 year old men in Viborg County and thus a substantial number for a subgroup analysis. The relative reduction of AAA-related mortality was 0.36 [95% C.I.: 0.14;0.93] similar to the overall relative reduction of AAA-related mortality of 0.34 [95% C.I.: 0.20;0.57]

5.3.2.1.2. Benefit of high and low risk screening for AAA

After seven years of follow up, the relative reduction of AAA-related mortality among those in high risk was 0.22, similar to 0.24 in the low risk group. Of course, cardiovascular and pulmonary comorbidity affects survival, and thus the observed findings after 7 years could have changed after 14 years of observation. A tendency was indeed noticed with a reduction in AAA related mortality of 0.29 [0.14;0.61] in the low risk group compared with 0.42 [0.20;0.88] in the high risk group, which could reflect better overall survival, few not offered repair when needed, and with lower risk of surgery. The difference is obviously not significant, but suggests screening men in low risk of AAA is more efficient than those with AAA-associated diseases. However, it is the absolute risk reduction and saved living years with ultimately determines the final cost effectiveness of high risk versus low risk screening.

5.3.2.1.3. Lower operative risk of screen detected cases

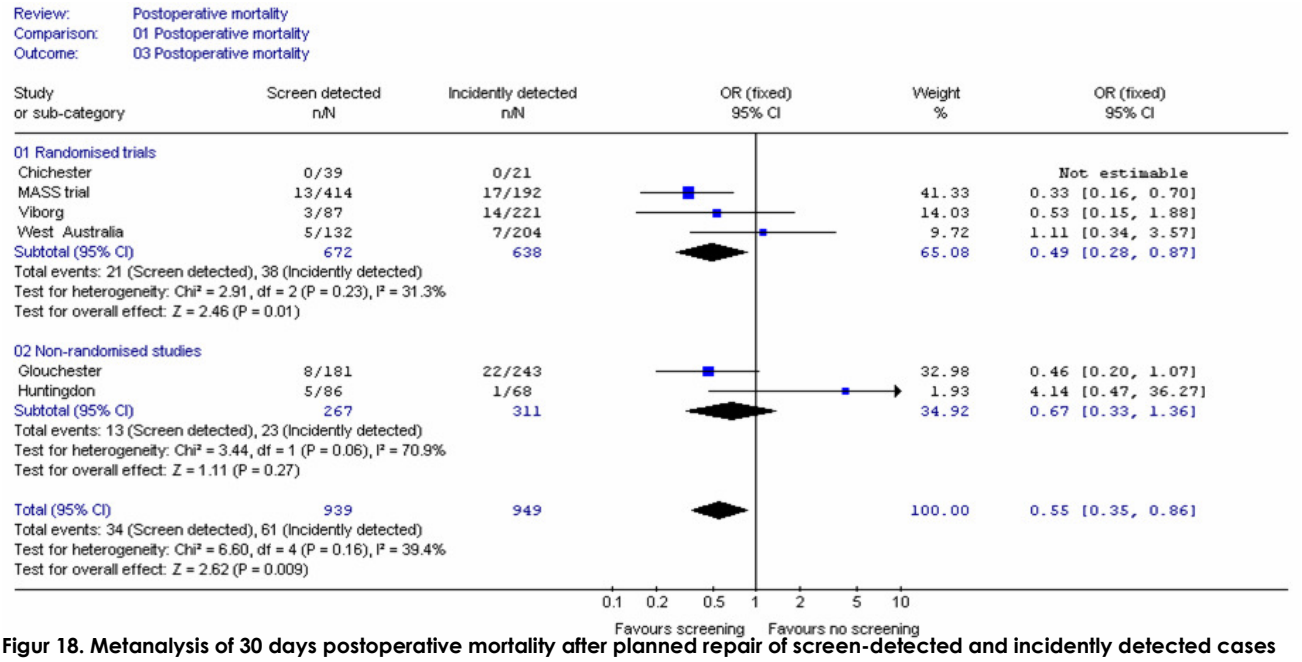
We have previously reported that operations for screen-detected AAAs had fewer complications than non-screen detected AAAs[401]. Later, the permanent Gloucester screening program reported lower mortality from operations of screen-detected than from non-screen-detected AAAs[194]. Both findings may be due to selection, and perhaps also to earlier surgery in screen-detected cases which will produce a group of more fit patients. However, in an earlier report, we found no sign of lower age at surgery in the invited group. Nevertheless, the planned operations in the invited group were of shorter duration, less blood consuming and tended more often only to require an aortic tube. Although these factors are all associated with fewer complications, the frequency of complications was not significantly lower than in the control group[402]. The study revealed that the frequency of complications remained high: 29% in the invited group and 37% in the control group. However, a trend was noticed, and it seems likely that screening may reduce complications and peroperative mortality in the long run; in the large randomised multicentre aneurysm screening study [MASS], the 30 days postoperative mortality in the screening group was 4% compared with 8% in the control group. However, even this large study [N>60.000] did not report statistical significance - probably due to the relatively low frequency of operations and relatively low peroperative mortality rates with consequently poor power of the analysis [335]. The CASS collaboration between the Chichester trial, the MASS trial, the Western Australian Trial and the Viborg Study could answer this question in the future[147]. However, a clear indication is observed when the postoperative 30 days-mortality of incidently detected cases are compared to screen-detected cases in the MASS trial. It shows significantly three times higher odds for dying within 30 days from planned surgery in incidently detected cases compared to screen-detected cases. Consequently, a metaanalysis have been performed including updated data from The Western Australian Screening Study, The Huntingdon Screening study, and Viborg Study, together with reports from other screening trials and programmes has been performed. Among 939 planned repairs of screen-detected AAA died 35 [3.7%], while 61 [6.4%] of 949 planned repairs of incidently diagnosed cases died within 30 days postoperatively [OR=0.55, 95% C.I.: 0.35; 0.86] [Figure 18, not yet published].

This indicates that men with screen detected AAA are considerably more fit for surgery than incidently detected cases. In a way, this may also seem logical; incidently detected cases are detected due to health problems, often related to decreased survival as lower limb ishaemia, and cardiac disease, while screen detected cases have undergone a completely different selection. They attended screening for AAA, probably after considering themselves fit for surgery, attenders to screening for AAA have better survival than non-attenders [I], and most of them were operated after surviving and attending a surveillance period. Consequently, screen-detected cases may have a different survival than incidently detected cases.

The finding is important as national differences in costs and benefits may exist, and a need for national evaluations could be demanded from national health authorities, which would request local ecomonic modelling. Such modelling requires assumptions on long term survival and quality of life after surgery. The postoperative quality of life after surgery for screen-detected AAA is only examined for one year, and described similar to the background population with six different tools[15;164].

5.3.2.2. Cost effectiveness of screening

Selection bias seems hardly possible, since it is population-based, and the attendance to screening and the prevalence of AAA is comparable to most studies. However, if screening was to be introduced, it would be offered med aged 65 as a once in a life time offer. The question is whether results from this and similar randomised trials can be generalised to that group.



Figur 18. Metanalysis of 30 days postoperative mortality after planned repair of screen-detected and incidently detected cases

Do to five new generations in target for screening were uniquely recruited to this study, a relatively high number of men below 66 years were recruited, allowing a subgroup analysis. The subanalysis of men aged 65 years indicated a higher ICER at 1,308€ due to a minor increase in the average incremental cost of providing the screening programme, and the mortality benefit was reduced from, on average, 0.08 life years to, on average, 0.07 life years. As recruitment of these new generations in target for screening first ended in 1998, this may be due to the shorter observation time, and the cost effectiveness increases with time, as noticed in the sensitivity analysis [Figure 17] in combination with a smaller proportion of large AAA at baseline, which increases the length of surveillance before the AAA becomes in risk if rupture.

Information bias seems very likely, since a man with known ischemic heart disease dying suddenly of a ruptured AAA, cause of death is like to be classified as a heart attack, while on the opposite, a man with a known AAA suddenly dying of ischemic heart disease, the cause of death is likely to be misclassified as caused by ruptured AAA. In order to minimize this, an independent end point committee validated the official causes of death by reading all available notes concerning the deaths. However, this is still potentially biased against screening. Consequently, the primary outcome for the economic analysis was all cause mortality since it avoids such bias.

The screening costs were 30.95€ per invited which is similar to the MASS trial [30.58€]. However, information bias may have happened concerning the estimation of the costs of AAA repair. The estimation of the costs for AAA repairs revealed 3 outliers[304]. These outliers were the consequence of major wound and intestinal consequences due to modern treatment with abdominal decompression and vacuum assisted closure of large abdominal defects[108;403]. Excluding these from the analysis, the estimated ratio of costs for ruptured versus planned repair of about 2.0 compares very well to the numerous of studies made in the past[192;404]. However, these were performed before this new approach for severe wound complications. Consequently, we may be wrong in the exclusion of these three cases – if so, the cost effectiveness of screening would be very attractive saving 734€ per gained QALY.

In addition, the cost analysis considered only the first year of AAA-related surgery. If any of participants experienced subsequent episodes of surgery the cost would be underestimated.

Confounding of the trial seems unlikely since it is a randomised trial, where the age between the intervention group and the control at entrance were similar, indicating a successful randomisation.

The other subgroup analyses of individuals with high and low risk or increasing the screening costs showed no great influence on the cost-effectiveness ratio.

Comparison with other similar trials is difficult since only the Chichester group have reported 15 year results[333]. The Chichester trial experienced only a 11% reduction in AAA related mortality after 15 years, and has never reported any cost effectiveness analysis of the results. The design of the trial had several differences than the presented one; it recruited men up to the age of 80, the size criteria for offering planned surgery was 6 cm, in stead of 5 cm in ours, and long term compliance showed to be difficult for the trialists to handle.

In a recent long term prognosis from the MASS trial based upon the initial 4 year results, the cost per saved living year after 30 years would be £2,320 [25,056 DKr], which seems quite attractive, especially taken their conservative assumptions, as ours [I], for the model into account[405].

The MASS trial also reported the cost-effectiveness after seven years of follow up. The costs were estimated to be $19,500 [DKK 106,275] per life-year saved based on AAA-related mortality and $7600 [DKK41,420] per life-year saved based on all-cause death[335]. Consequently, an extensive improvement in cost effectiveness is noticed, so it is more comparable with the cost effectiveness observed after five years in the Viborg Study[406] but the benefits concerning prevented deaths and emergency operations seem higher in the Viborg Study compared with MASS trial. Recently, the MASS trial published 10 year results. The hazard ratio was 0.52 [95% C.I.: 0.43; 0.63] for AAA-related mortality in the group invited for screening[335]. However, no end point committee had reviewed the causes of deaths, which were only based upon ICD codes, and thoracic cases were included, so it must be assumed to be biased against screening. The MASS trial also reported the cost-effectiveness after 10 years of follow up. The costs were estimated to be £7600 [66,500 DKK] [£5100 to £13 000] per life-year saved based on AAA-related mortality but no estimations were based on all-cause death, as when they reported their 7 year results, making the results difficult to compare. Nevertheless, screening for AAA seems cost effective in both studies. The studies clearly emphasizes that the cost effectiveness improves over time, which is quite natural, as screening costs are mainly at baseline, but ruptures happens over the long following period. Consequently, further improvements can be expected especially in the MASS trial.

5.3.2.2.1. The Danish Health Technology Assessment of screening for AAA

The cost effectiveness of these two randomised trials is in extreme contrast to a recent health technology assessment in Denmark where the costs per gained living year in a model were estimated to be above 400,000 DKK without quality of life adjustment[316], while other recent modelling studies have reported corresponding estimates around 45-65.000 DKK[181;202;314;407;408] The explanation for the divergence across modelling studies could be a difficult field to modelling, and lack of original estimates beyond the follow up time of the RCTs; in particular, modelling studies obviously cannot surpass the quality of the study mass from which their parameter estimates are built. Consequently, such models always have to rely on the validity of the Markov decision tree behind the model and the assumptions behind the model, and these are controversial and flawed in the Danish HTA model.

5.3.2.2.1.1 The Danish HTA model does not reflect reality

The HTA model is a progression model of AAA where it can be small, medium or large. Each step has a possibility of rupture, and the small and medium sized AAA also have a probability of progression to the next step. The risk of rupture of "large" AAA is 6.5% annually based upon the observed risk of rupture in 5-6 cm AAA kept under surveillance in the UK small aneurysm trial[96] – however, as the trial name indicates – it doesn´t have data concerning large AAA. Consequently, the model does not include large AAA sized above 6 cm - the possibility of aneurysmal progression simply stops at 6 cm, while it is basic knowledge that the expansion rate increases with size as well as the risk of rupture [see table 3]. Actually, based upon randomised trials vascular surgeons first starts to take AAA seriously at the size of 5.5 cm in order to prevent rupture[68],[69]. This error appeared the first time in the economic model performed by Silverstein et al. in 2005[407]. In addition, as the assumed emergency repairs are based upon the risk of rupture in the UK SAT trial[96], the model does not include cases having emergency repair without rupture. These cases constitutes one third of all emergency cases performed in Denmark, are encumbered with three times higher morbidity and mortality than elective cases [www.karbase.dk], and are prevented as ruptured cases by screening[334]. This error appeared the first time in the economic model performed by the Swedish HTA economist Henriksson et al in 2005[202].

Consequently, only 0.86% of the all deaths in men above 65 years are caused by AAA in the non-screened group. No epidemiological study has ever reported such a low proportion but mostly around 2-3%[45-49;52;54-63]. In the metaanalysis, AAA related deaths caused 2.8% of the deaths among those not invited to screening [Figure 18]. In contrast to the MASS trial, the Danish proportions are based upon validated causes of death, and not the crude ICD codes, so the proportion in the crude official Danish registry of causes of deaths is higher. In addition, the proportion is known to increase with age [See table 2]. In all, the lack of emergency repaired cases without rupture and large AAA above 6 cm leaves the model without any external validity.

5.3.2.2.1.2. HTA cost units for surgery do not reflect the actual costs

The HTA authors are using the HRG tariffs 0513, 0514, and 0515 as estimates for the costs of AAA repair in Denmark. However, the used HRG tariffs are only the costs which can be reimbursed by the vascular department [See table 10]. The actual hospital costs [see table 9] can be divided into:

A. Costs before submission to the vascular department

The used HRG tariffs do not include preoperative costs as CT scan [HRG: PG10C], consultation at the outpatient clinics [HRG tariff: BG50C] and costs at the primary receiving department in case of emergencies

[HRG: 0550], or costs for emergency transports between receiving and operating hospitals [Http://visualdrg.sst.dk/2006/].

Consequently, these costs are not included in the cost units used by the HTA authors.

B. Stay at the vascular department

During the stay at the vascular department, the intensive care units have independently since 2005 reimbursed the costs for stays exceeding 48 hours [which is more the rule than the exception in ruptured cases] with the HRG tariffs: 2632 [7,281£], 2633 [16,439£], 2634 [31,083£], 2635 [81,471£]- depending upon the number and degree of failing organs. Compared to the vascular HRG tariff of 12,125£ for survivors, these tariffs are quite high. [Http://visualdrg.sst.dk/2006/]. These costs are neither included in the cost units used by the HTA authors.

C. Costs after the stay in the vascular department.

Discharge from the vascular department to other departments for treatment of complications or postoperative care before final discharge to home or nursery homes are neither included, and the departments receiving the patients reimburses with their relevant HRG tariffs. Finally, readmissions later due to complications is neither included nor are postoperative outpatient costs.

D. A flawed use of HRG code 0513 [Death within 48 hours after surgery]

In addition, a serious flaw in the use of the HRG tariffs in the study has occurred; because HRG code 0513 [Death within 48 hours after surgery] is used for surgery for deaths occurring within 30 days [Http://visualdrg.sst.dk/2006/].

In all, operation for rupture is assumed to be cheaper than elective surgery. This has never been reported before[186;192;202;304;306;308;308;404], and as our estimation of the actual costs indicate305, causes a substantial bias against screening.

A vascular expert in HRG tariffs associated with the HRG unit at the National Board of Health appointed by the Danish Society of Vascular Surgery, Leif Panduro Jensen, actually informed the HTA authors at a public symposium the 9th of December 2008 of their above mentioned mistakes. Regardless of this critisim, the authors published the model without any correction in BMJ half a year later[408].

5.3.2.3. Future perspectives

However, in the end, these present cost effectiveness analyses and considerations are probably already outdated because statins and aspirin seem capable of reducing the growth rate of AAAs[409]. This will prevent later elective surgery for AAA in early detected cases. Such operations count for the majority of the costs in the invited group.

In addition, AAA patients will presumably survive longer owing to the preventive benefits of aspirin and statins. Furthermore, the costs of acute surgery can be expected to increase as treatment for abdominal compartment becomes a routine procedure[107;108].

A modern screening programme for AAA should definitely include general cardiovascular prophylaxis [See study VII]. When such actions are taken, it is a natural question to ask, whether we should search for other silent atherosclerotic lesion. Decreased ABI is associated with three times higher mortality, is asymptomatic in 50-66% of the cases, most frequent in older men, and can by detected by non-invasive Doppler-supported blood pressure measurement within few minutes.

5.4. AAA-wall calcification association with the growth rate and later surgery. In addition, to examine whether such calcification is associated with future cardiovascular events and death[IV].

5.4.1. Major findings

In spite of its obvious potential importance for the strength of the AAA wall, the role of calcification of the AAA wall seems not to have been investigated in small AAA.

However, in all the patients with a screen-detected AAA in the Viborg Trial in 1994, the calcification degree was judged to be above or below 50%. The intraobserver reproducibility was estimated to be 84% [95% C.I. 70-93%].

The initial AAA size was significantly lower in men with an AAA wall calcification above 50% and the overall median growth rate was significantly lower in men with an AAA wall calcification above 50% [1.72 mm/year vs. 2.97 mm/year, Wilcoxon´s rank sum test: P=0.001]; a significance that persisted after multivariate linear regression analysis adjusting for smoking and aspirin use. In addition, a total of 12 men with an AAA calcification above 50% were operated compared with 25 men with an AAA calcification below 50%. Consequently, the operation incidence ratio was 0.35 [95% C.I.: 0.18-0.71] in cases with a calcification degree above 50% [P=0.003, Figure 19]. This statistically significant difference persisted after adjustment for age, smoking and use of aspirin [risk ratio: 0.36 [95% C.I.: 0.18-0.74].

A total of 33 [54%] men with AAA calcification above 50% experienced a cardiovascular caused admission to hospital during the observation period compared with 22 [33%] among men with an AAA calcification below 50%. This difference was statistically significant by the chi square test [P=0.029], but statistically insignificant by Cox regression analysis adjusting for age [risk ratio 1.64 [0.94-2.87] P=0.083, Figure 20]. This may be due to confounding by age and/or insufficient power of the analysis, since a 64% higher age-adjusted risk wasn´t statistical significant, so a tendency could be present. In spite of this tendency,

the age-adjusted mortality rates between the two calcification groups were similar: hazard ratio: 0.89 [0.56-1.40], P=0.604.

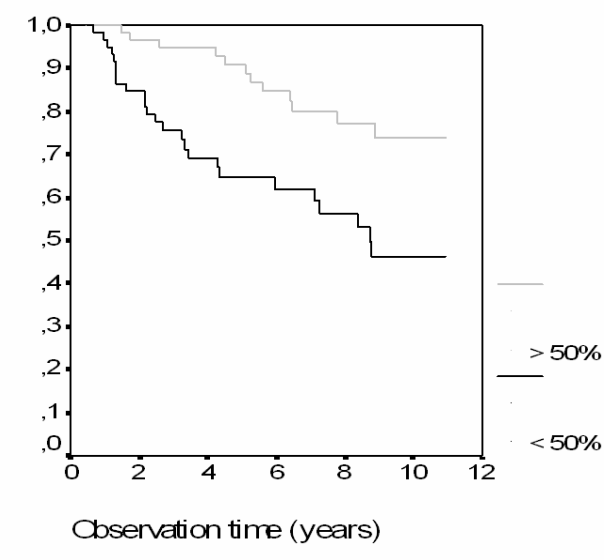


Figure 19. Survival curves for operation for AAA in men with small AAA in whom calcification encompasses more or less than 50% of the maximal circumference

5.4.2. Discussion of major findings in study IV

5.4.2.1. Mechanism behind the association

The question whether the mechanism is mechanical/physical or reflects different dominating pathogenetic pathways remains unsolved. In 1998, the patients alive with intact AAA had the elasticity and stiffness of their AAA walls determined by an echo-tracking ultrasound system[222]. There were no significant differences in wall elasticity or stiffness between AAAs in which more or less than 50% of the circumference was calcified. However, the variability of the measurements was substantial[410] and the numbers examined were small, so the result may represent a type II error. However, the values are so equal that a non-mechanical explanation of the association between the degree of wall calcification and the clinical course of small AAA seems most plausible.

5.4.2.2. Comparable studies

Shortly after the paper was accepted, a publication from one of the groups working with finite element analysis published a paper dealing with the role of calcification on wall stress utilizing patient-specific finite element wall stress computations. Areas of calcification were defined node-wise in the mesh of the model, quantified, and expressed as a calcification index. A weak positive correlation between calcification index and peak stress was reported. They conclude that the relative amount, location and shape of the calcified regions may influence the effect on AAA wall stress. The work is interesting but not supported by clinical data, and an earlier attempt to relate wall calcification with rupture could not find a relation[230].

Another retrospective study demonstrated an association with hypertension, coronary artery disease, and peripheral vascular occlusive disease in 129 cases with large AAA and wall calcification above 40% of the circumference judged by CT scanning [229].

The present study could not confirm this after adjusting for age, but a trend was noticed.

Concerning the association between AAA wall calcification and the progression of small AAA, there seems not to be any comparable reports. The findings suggest the calcification degree of the AAA wall may hold a seldom strong predictive value for the clinical course of small and middle-sized AAAs, but the major limitation of the study is the interobserver variation of the calcification judgement is unknown. Consequently, the findings of the present study request confirmation, and future work could take advantage in creating a computer-assisted technology as seen in cardiology, where the computerised calcium score judged by CT-scanning has proven be predictive for further cardiovascular events[411].

A similar technology in AAA-wall calcifications in small AAA could produce a more precise and nuanced determination of the degree of calcification.

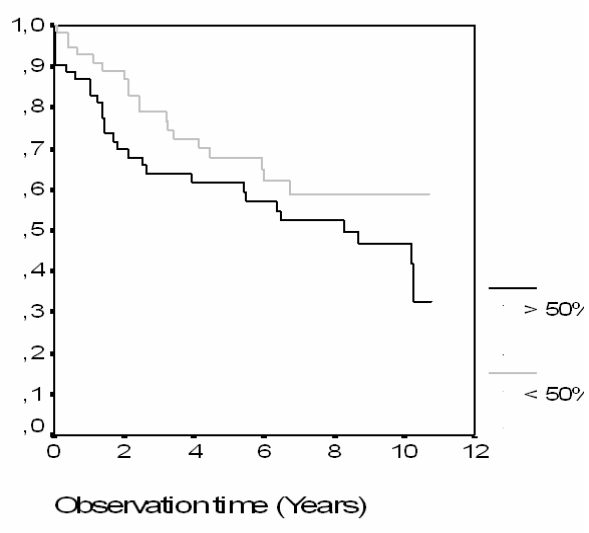


Figure 20. Survival curves for admission to hospital due to cardiovascular events in men with small AAA where calcification occupies more or less than 50% of the maximal circumference

5.5. THE POTENTIAL PATHWAYS IN THE PLASMIN ACTIVATION ASSOCIATED WITH THE PROGRESSION OF AAA, AND THE POTENTIAL ROLES OF SMOKING, HOMOCYSTEINE, IGA-CP, MAIF, AND TGF-BETA-1 IN THESE PATHWAYS [STUDY V].

5.5.1. Major findings in study V

Plasmin plays a central role in the aneurysmal progression as being a common activator of the three

other proteolytic systems involved in the degradation of aorta[272;273], and has been associated with aneurysmal expansion rate[275]. An interesting question is to clarify the activating pathway of this apparently key protease in the progression of AAA, and triggering factors of this pathway.

Consequently, we recently studied the potential pathways for the activation of plasminogen associated with the progression of AAA.

We found [V] a mean annual expansion rate of 2.7 mm, and a significant positive correlation between aneurismal growth rate and tPA [Rho= 0.37, P=0.004, Figure 21], but surprisingly not between the aneurismal growth rate and uPA [Rho=0.001, p=0.993].

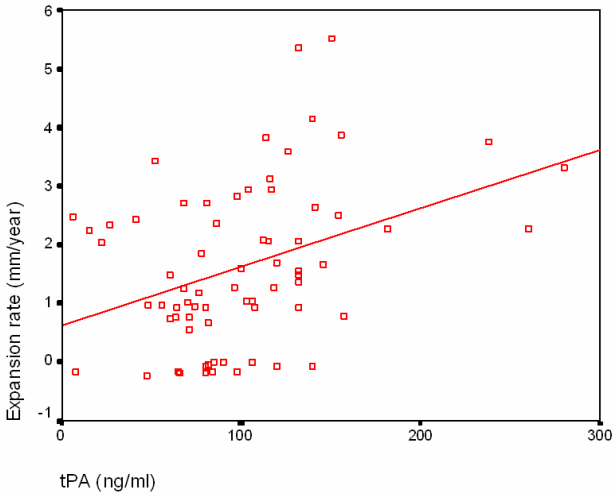


Figure 21. Scatter plot of the correlation between P-tPA and the annual expansion rate of small AAA. Spearman's Rho= 0.37 [P=0.002][V].

We also found [V] positive correlations between S-Cotinine and tPA [Rho=0.238, P=0.049], and S-Cotinine and the expansion rate [Rho=0.234, P=0.038]. No significant association between antibodies against C. pneumoniae were associated with tPA or uPA, but with the AAA growth rate [Rho=0.290, P=0.006]. No significant associations were noticed concerning homocysteine, MaIF, and TGF-β1 [Table 16].

5.5.2. Discussion of the major findings in study V

5.5.2.1. Association with tPA and not uPA

A significant correlation between tPA and progression rate was noticed, and surprisingly not uPA which usually dominates plasmin-mediated matrix modulation. This may be due to long-lasting binding of uPA to their specific receptors on the cell membrane which prevents inactivation of uPA, but inhibits relevant systemic detection of biological active uPA. However, the result seems to be in agreement with the observations by Reilly et al.[412;413]. They found elevated fibrinolytic activity in AAAs compared with normal and atherosclerotic aortas by fibrin autography, and that the majority of this activity was caused by free tPA; but uPA was detected as well, but in insignificantly higher concentrations. They also did a immunohistochemistry study, which showed that in normal aortas tPA was only present in the intima, while tPA was diffusely present in the intima and media of AAA walls. UPA was only present in the monocellular cells in the infiltrate associated with the adventitia in AAA walls.

Recent studies from the Bichat Hospital in Paris have addressed interesting new views of this association. They separated the luminal, intermediate and abluminal mural thrombus layers, as well as media and adventitia, and incubated them in cell culture medium, and measured various plasminogen activators and inhibitors as well as plasmin and D-dimers release. In parallel, mRNA expression analysis was performed, and completed by immunohistochemical localization of these components in AAA. All fibrinolytic system components were present in each aneurysmal layer. However, the mural thrombus was the main source of active serine-protease release where, the luminal layer of the thrombus released greater amounts of Plasmin and D-dimers. In contrast, but in agreement with the Reilly study, mRNA expression analysis showed an exclusive synthesis of tPA and PAI-1 within the wall. These results suggest that the association between plasma concentrations of PAPs and AAA progression rate could be related to proteolytic activity of the mural thrombus.

The role of uPA in AAA remains unsolved. The negative correlation with AAA-size and the missing correlation with aneurysmal progression could indicate that the role of uPA is most present in small AAA, and the role is not matrix degradation causing dilatation. As mentioned, Reilly found that uPA was only present in the monocellular cells in the infiltrate associated with the adventitia in AAA-walls[412;413]. This localization could indicate a role in the neoangiogenesis also observed in the aneurysmal development, a role which also has been suggested by Scheiderman et al.[414]

5.5.2.2. Lack of asscoiation to MaIF and TGF-β1

MaIF levels did not significantly correlate with expansion rate [p=0.06], in contrast to an earlier reporting in collaboration with Havard University[415]. This may be due to the relatively low numbers studied, a relatively high frequency of cases with MaIF-levels below the detection border which impairs non-parametric tests, and a relatively high CV. If the MaIF-levels were transformed with the natural logaritm, the distribution became fairly normally distributed. In that case Pearson´s correlation coefficient became 0.25, with a p-value of 0.038. The almost lack of any correlation with tPA [rho=-0.05] suggests also another pathway for this cytokine.

TGF-β1 is suspected to activate tPA and PAI-1 but we were not able to demonstrate any associations. However, the variation of the measurements of TGF-β1 and aortic size combined with the pollution of TGF-β1

originating from non-aortic locations could hide a weak correlation.

5.5.2.3. Potential non-operative treatments

As mentioned, operation for AAA is encumbered by a substantial risk of complications and death, and carries the far most economic burden by offering screening. However, the majority of AAA diagnosed by screening is too small initially to be recommended for operation. The early detection allows general cardiovascular prevention to be taken, which could be beneficial due to an expected higher mortality, and efficient medical inhibition of aneurysmal progression could prevent later AAA-repairs. In all, it would be of benefit for the patient, and could improve the cost effectiveness of screening substantially. The present study deals with the potential benefits of smoking cessation and vitamin supply due to hyperhomocysteinaemia which is discussed below, but for complete cover of the present potentials, lipid lowering, antioxicidants, and alohol consumption are also discussed.

5.5.2.3.1. Smoking cessation

Smoking is one of the most constantly mentioned risk factors for AAA in case control studies[43;212;351;355;356;358;416-419]. This association could be due to the high frequency of coexisting morbidity. However, the many cohort studies reporting an AAA expansion rate do not associate smoking with AAA growth. This may be due to a weak correlation or to the use of unreliable data obtained by interviews, which could be avoided by performing cotinine measurements[355;419;420]. Apparently, only two studies have prospectively associated smoking with aneurysmal growth rates[420;421].

We also found [V] positive correlations between S-Cotinine – a nicotine metabolite - tPA and the expansion rate suggesting that smoking is participating in this pathway. This is in accordance with the performed multiple linear regression analysis adjusting for S-Cotinine, the correlation between tPA and expansion rate remained significantly correlated, while S-Cotinine failed to reach significance and vice versa if the sequence of independent variables was reversed.

In addition, we found in a recent multivariate analysis of interview data, we also found [not yet published] that current smoking was associated with increased aneurismal growth rate in cases with an AAA below 40 mm and with 40-49 mm in diameter. Low dose aspirin use, Charlson score[422] and educational level were additional, independent variables. Among non–smokers, the AAA growth rate was on average 0.85 mm [95% C.I.: 0.24; 1.47] lower per year in cases with an initial AAA below 40 mm in diameter and 3.52 [95% C.I.: 1.80; 5.23] mm lower per year in cases with an initial AAA initially of 40-49 mm. The risk ratio for later operation due to expansion among non-smokers with an AAA initially sized 40-49 mm was 76% lower than among current smokers in a Cox regression analysis adjusting for low dose aspirin use, Charlson score and educational level [risk ratio for non-smokers: 0.24 [95% C.I.: 0.08; 0.76].

The overall conclusion is that smoking cessation seems to be a powerful tool for reducing aneurismal progression and need for later repair, but if complete cessation is not possible, the linear association between growth rate and S-cotinine suggests that benefits could be achieved just by reducing the amount of smoking.

5.5.2.3.2. Vitamin supply

The systemic concentration of homocysteine in aneurysmal cases is reported to be increased compared with that in controls[423-426]. There is a polymorphism in the MTHFR gene involved in the homocysteine metabolism. Strauss et al. have demonstrated a significantly elevated T allele frequency in AAA patients, and an OR for AAA of 4.4 if a T allele is present in the genotype[427]. However this could not be confirmed by the group of Van Rij, but they did find a significant association between the T homozygotes and the size of the AAA[428].

Case control studies have found increased levels of homocysteine in AAA patients but proper confounder adjustment have to include creatinine clearance. This was done by Peeters et al. They could not find any association[429]. We could not find any trend that the level of homocysteine correlates with aneurysmal expansion [Rho=0.063, P=0.535]. There is apparently only one comparable study, and they could correlate the level of homocysteine with the growth rate of small AAA. A multivariate analysis was performed for growth rate vs. homocysteine, hypertension and hypercholesterolaemia. It showed homocysteine to be the only significant factor affecting AAA growth rate [R=0.28, p=0.003]. However, they did not adjust for smoking and renal function[430]. The finding is in contrast to our study, and to research findings from other cardiovascular diseases; that increased levels are noticed but intervention with reduced homocysteine does not influence the risk of cardiovascular events[431].

Recently, no significant differences in the frequency of the MTHFR C677T variant causing hyperhomocysteinaemia was found between AAA patients and controls[428].

In all, evidence of a beneficial role of vitamin supply to impair AAA progression is sparse.

5.5.2.3.3. Lipid lowering diet or drugs?

Dyslipidaemia and Lp[a] levels have been associated with atherosclerosis. Some case control studies have observed increased levels of various lipids in AAA patients, while others have failed to do so[30;360;424;432-435]. Disturbances in lipid metabolism are treatable, but the role of such disturbances in AAA progression is largely unknown.

	tPA	uPA	PAI1	MaIF	TGF-β1	Homo-cysteine	Cotinine	IgA-CP
Growth rate (mm/yr)	0.368* (0.002)	0.001 (0.993)	0.015 0.871	0.224 (0.061)	0.000 (0.999)	0.063 0.535	0.234* (0.038)	0.290* (0.006)
tPA (ng/ml)		0.125 (0.308)	0.328* (0.006)	-0.046 (0.703)	-0.002 (0.984)	0.091 (0.414)	0.238* (0.049)	0.135 (0.252)
uPA (ng/ml)			0.005 (0.966)	0.119 (0.419)	-0.082 (0.570)	0.048 0.691	-0.345* 0.006	-0.053 0.690

Table 16. Non-parametric correlation matrix between between activators and inhibitors of plasminogen, and the progression of small AAA. Spearmann´s correlation coefficients. P-values in parenthesis.

We have not found that cholesterol, HDL, LDL, or Lp[a] influences the progression of AAA[111]. Similar observations were later made in the UK small AAA trial[421;436].
The lack of any correlation with aneurysmal expansion in the large UK study [N= 1,743 followed for two year in average] in particular may indicate that pathogenetic factors differ in atherosclerotic and aneurysmal progression.

5.5.2.3.4. Antioxidants

In theory, free oxygen radicals oxidise LDL could regulate MMPs and induct apoptosis of vascular smooth muscle cells-key components in AAA development [437].

However, in the Viborg AAA cohort, we found no association between Ab-oxLDL and the AAA growth rate[436]. In addition, Vitamin E and beta-carotene are important antioxidants, and the level of vitamin E has been reported to be decreased in AAA patients.

However, in 29,133 50-69-year-old male smokers were randomised to a supplement of vitamin E, beta-carotene, both or placebo and followed for 5.8 years for ruptured AAA and planned AAA operation, all results were in favour of a benefit of antioxidants, but all statistically insignificant. The strongest association was the reduced risk of ruptured AAA among vitamin E supplemented men [RR 0.71 [CI: 0.48-1.04][438].

5.5.2.3.5. Alcohol consumption

Recently, a prospective, biennially updated data for a cohort of 39,352 US men from 1986 to 2002 was reported by the Havard University. The association of incident AAA diagnosis with alcohol consumption in grams per day was assessed at baseline and by using alcohol consumption data updated every 4 years, controlling for previously reported cardiovascular risk factors. Updated alcohol consumption data showed the hazard ratio for the highest level of intake [> or=30.0 g/day] was 1.65 [1.03, 2.64][359]. The finding has been confirmed by some, while others could not find any association[43;348;359;396].

5.5.2.4. Other risk factors for expansion

A small AAA, i.e. less than 5 cm in maximal, diameter expands on average 2-4 mm annually but with considerable variation. AAA size [diameter, cross sectional area and volume], smoking, hypertension, LDL, COPD, age, severe cardiac disease, previous stroke and female gender have been reported to be associated with increased rate of expansion, while coexisting intermittent claudication and diabetes have been shown to be associated with a lower expansion rate[85;249;420;421;436;439-449]. The most powerful study, the UK small AAA study, monitored 1743 patients with AAAs for a mean of 2 years, and Brady concluded: "Baseline diameter was strongly associated with growth. AAA growth rate was lower in those with low ankle/brachial pressure index and diabetes, but higher for current smokers [all P<0.001]. No other factor [including lipids and blood pressure] was associated with AAA growth"[421]. They did not test LDL.

We found a mean annual expansion rate of 2.7 mm [V], that approximately one third expanded to above 5 cm in diameter within 10 years depending on the initial AAA diameter [II], and that smoking was associated with an increased expansion rate and later operative repair due to expansion [V].

We have been unable to demonstrate an association between growth rate and age, educational level, Charlson score[422], steroid treatment, various lipids including LDL, homocysteine level, pulmonary function, systemic blood pressure, coexisting hospital- diagnosed atherosclerosis and ankle brachial blood pressure index[63;249;436;444;450][V].

5.6. DETECTION OF OMP IN AAA WALL TISSUE BY USE OF PURIFIED CPOMP ANTIBODIES FROM AAA PATIENTS AND SEARCH FOR POTENTIAL CROSS-REACTING PROTEINS IN THE WALL OF AAAS [STUDY VI].

5.6.1. Major findings

C. pneumoniae has been demonstrated in AAAs by immunohistochemical techniques, and PCR. However, the validity of the methods is questioned, and intervention trials with macrolides have been disappointing but as shown in study V, antibodies against C. pneumoniae are associated with the clinical

course of AAA. Consequently, we decided to isolate C. pneumoniae antibodies from AAA patients and to examine what they reacted on in aneurismal walls by two dimensional gel-electrophoresis, immunoblotting and mass spectrometry. This technique would allow us to confirm the presence of OMP in the AAA wall, if present, and if not, what the antibodies against C. pneumoniae from men with AAA really reacts on in the AAA-wall.

After purification of the antibodies against C. pneumoniae from AAA patients, we checked that the recovered antibodies still possessed the OMP reactivity by Western blot analysis of pure recombinant OMP. As demonstrated in Figure 22 [lane 1], recombinant major OMP runs in a silver-stained gel as a single band of 40 kDa. Immunoblotting was performed by use of the affinity-purified anti-OMP antibody [lane 2]. A strong signal was obtained, corresponding to 40 kDa. Two very faint, higher-molecular-mass bands were also observed on the Western blot. These may be because of small amounts of aggregates of the recombinant protein or because of small amounts of impurities in the protein sample cross-reacting with the antibody. Immunolabeling controls performed by use of anti-OMP preabsorbed with the recombinant OMP exhibited no labeling [not shown].

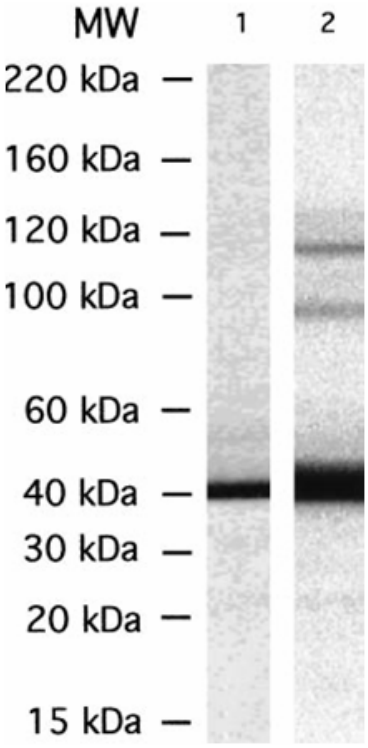


Figure 22. Immunoblot analysis of affinity-purified Cp OMP antibody. Lane 1. Pure recombinant OMP was electrophoresed and silver-stained. Protein is very pure, with only 1 band present at 40 kDa, as expected.
Lane 2. Western blot of pure recombinant OMP reacted with affinity-purified anti-OMP antibody, showing that anti-OMP reacts with OMP antigen.

We then investigated whether we could detect the presence of OMP in the AAA wall from 17 patients by use of the anti-OMP antibody. Western blots with AAA homogenate and anti-OMP antibody are shown in Figure 23. No specific reaction was seen at 40 kDa according to the molecular mass of OMP. Only patient 12 showed some reactivity at 40 kDa which may be due to presence of OMP. However, a much stronger general reaction [also from patient 12] was seen with cross-reacting proteins at 50 kDa from all AAA patients. In addition, other less strongly reacting bands were noticed with still slightly higher molecular masses. The reaction was equally strong irrespective of age, current smoking, diagnosis of hypertension, and AAA size.

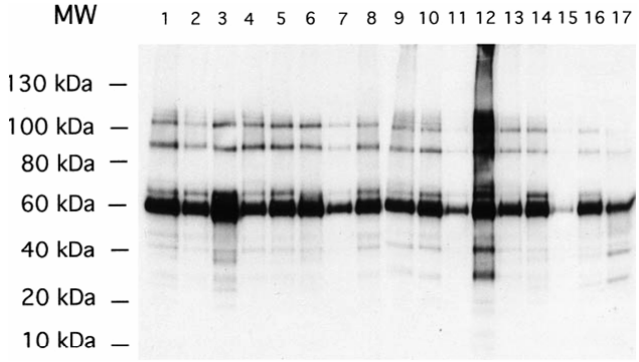


Figure 23. Western blot analysis of proteins from AAA wall proteins [lanes 1–17]. Blot was reacted with affinity-purified C. pneumoniae OMP serum antibodies. It was not possible to detect OMP as a 40-kDa protein. However, several crossreacting bands were found, especially one at 50 kDa, together with some minor bands with slightly higher molecular mass.

To identify the reacting proteins, we first performed a high-resolution purification of aortic wall proteins from 1 selected patient [patient 1] by 2D gel electrophoresis. One of the gels was Western blotted and reacted with the anti-OMP antibody, and the other gel was silver-stained and served as reference. By aligning the blot to the silver-stained gel, 3 proteins were cut out from the silver-stained gel.

The mass spectrometry analysis revealed the sequence of several peptides from each of the 3 proteins cut out. All peptides were found to be present in the heavy chain of

human immunoglobulin. In addition, it was specifically analyzed whether the proteins could originate from the C. pneumoniae OMP protein. This was not the case.

5.6.2. Discussion of the major findings in study VI

A tremendously interesting question is what has triggered the antibody response. If it was triggered by immunoglobulin, it may be due to an unspecific reaction between the horseradish peroxidase-conjugated secondary antibody [sheep anti-human antibody] and the present human immunoglobulins in the AAA wall[451;452]. However, in an earlier similar study, we applied commercial antibodies against C.

pneumoniae and found a cross reaction with haemoglobin, and no sign to an unspecific reaction between the horseradish peroxidase-conjugated secondary antibody [sheep anti-human antibody] and human immunoglobulins in the AAA wall[288].

Another possible explanation could be that the finding is a sign of AAA being an autoimmune disease. The only known antibodies reacting with immunoglobulins are rheum-factors, which are associated with autoimmune diseases. An autoimmune reaction has been suggested by others, and this hypothesis is supported by genetic susceptibility and histological examination of AAA walls, which shows an abundance of cells of chronic inflammation and Russell's bodies like in the autoimmune disease - Hasimoto´s thyroiditis. Furthermore, AAA walls also contain cytokines which modulate the immune response and activate proteolysis, and they demonstrate a substantial increases of IgG compared with aortic occlusive diseases and normal aortas[453-456]. In addition, homeostasis of the immune system is maintained by apoptotic elimination of potentially pathogenic autoreactive lymphocytes, and Fas-mediated apoptosis is impaired in activated lymphocytes from patients with autoimmune disease. Such apoptosis has been described impaired in AAA patients compared to patients with aortic occlusive disease and controls[457].

As mentioned, the polymorfies of human leukocyte antigen [HLA] is associated with autoimmune diseases[458]. Such genotypes are also associated with AAA; HLA DRB1*02 and B1*04 subtypes are reported to be more common in AAA patients than controls, and the B1*01, B1*08 and B1*14 alleles to be more frequent among the controls[459-461]. Similar findings were observed by Monux et al. but they failed to rearch significance[456]. In addition, another study on polymorphisms [HLA-DQA1, -DQB1, -DRB1 and -DRB3-5 alleles] in 387 AAA cases and 426 controls showed an association with the HLA-DQA1 locus among Belgian males, and found a significant difference in the HLA-DQA1*0102 allele frequencies between AAA cases and controls[462].

An autoimmune reaction could be triggered by an initial C. pneumoniae infection, explaining the fact that the antibodies react with OMP and apparently cross-react. An autoimmune disease instead of an infective disease has a dramatic impact on the choice of investigations of potential medical treatments because antiinflammatory drugs rather than antibiotics might be effective.

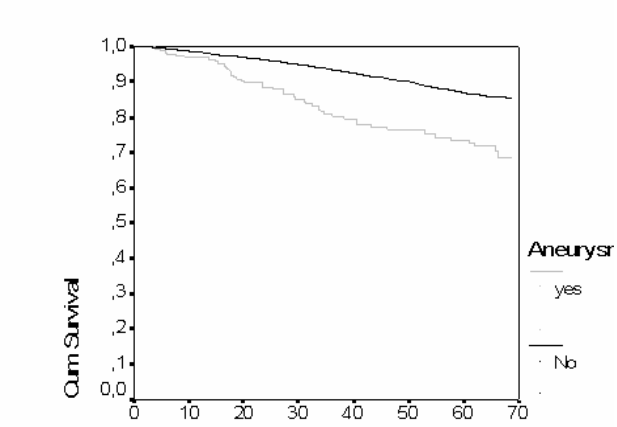
Future studies of this pathway could be directed toward other tissues in order to examine whether this observation is unique for AAA, and examining whether rheumatic factors are associated with AAAs and aneurysmal progression and whether

rheumatic factors cross-react with OMP.

Another really interesting topic would be attempts to identificy of what antigens the present immunoglobulins in the AAA wall react on.

5.7.1. Major findings in study VII

Patients with randomly detected AAA are known to have higher mortality than age-matched controls, especially due to cardiovascular diseases. If this is also true in screen-detected cases, ongoing screening could provide an opportunity to prevent morbidity and mortality from other causes through appropriately targeted intervention. Such intervention ought to be started during and after a diagnosis of cardiovascular disease or COPD. An important remaining question is whether men with screen-detected AAA not previously hospitalised with cardiovascular disease or COPD have a higher mortality due to these disorders and may therefore benefit from preventive actions.
During a median observation time of 63 months, we found [VII] an overall significantly higher mortality rate among men with AAA compared to men without AAA attending screening [Crude hazard ratio: 2.11; 95% CI: 1.73-2.59, P < 0.001] – after adjustment for age and a history of cardiovascular or COPD hospital admission [hazard ratio = 1.92; 95% CI: 1.43-2.58, P < 0.001 [figure 24]. This is not an unexpected finding, but still interesting since it describes the population mortality of AAA without the usual selection caused by random detection of AAA.



	0	10	20	30	40	50	60
+ AAA	191	185	161	142	132	116	99
- AAA	4625	4569	4112	3770	3668	3204	2737

Figure 24. Survival curves for men with and without AAA detected by screening.

Men with AAA had a significantly higher mortality both among those with and without previous hospitalisations for pulmonary causes [adjusted risk ratio=3.05; 95% CI: 1.19-7.83, P=0.020, and adjusted risk ratio=3.29; 95% CI: 1.78-6.08, P<0.001, respectively], but the absolute mortality risk difference for those without previous hospitalisation was just 6%.
More interesting was the finding of a significantly higher cardiovascular mortality in aneurysm patients without previous cardiovascular hospital discharge diagnoses compared with similar men without AAA [adjusted risk ratio=4.35, 95% CI: 2.73-6.94, P<0.001, Figure 25].

The cumulated five-year cardiovascular mortality among men with AAAs without previous cardiovascular hospital discharge diagnoses was 21%, and the absolute cardiovascular mortality risk difference after five years was 16%.

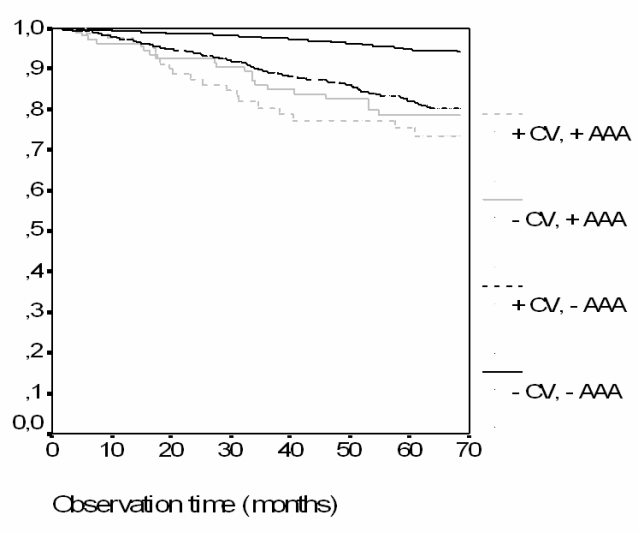


Figure 25. Kaplan Meier plots of cardiovascular-specific survival curves concerning groups classified according to presence or absence of AAA and a history of cardiovascular disease [CV].

5.7.2. Discussion of major findings

5.7.2.1. General cardiovascular prevention in men with AAA

The findings of excess cardiovascular mortality in men with AAA, who have never been admitted to hospital due to cardiovascular events strongly emphasise the need for general cardiovascular prevention in men with AAA, regardless of pre-existing comorbidity. Screening seems to be the only way to identy the majority of such cases. Consequently, a substantial additional cost effective benefit of identifying men with AAA by screening for general cardiovascular prevention seem possible - especially because of the availability of existing potent, low-risk preventive actions like smoking cessation, statins and low-dose aspirin. However, the actions must be cost effective. If the benefit of dietary instruction and 40 mg of simvastatin daily is as efficient as in the British Heart Protection Study [23], such simple action would save approx. 3.2% of all aneurismal patients from dying prematurely within five years. The Danish five-year costs of such a drug dose are DKK1,919 [Zocolip, 98 pieces= DKK103], corresponding to DKK59,968 per saved life [€8,049 or £5,636]. However, this will not be the net costs because the risk of suffering a major cardiovascular event is lowered, so that other hospital expenses are also prevented. There seems to be no comparable reports.

According to the new recommendations from the European Society of Cardiology such secondary cardiovascular prevention must include lifestyle intervention concerning smoking, relevant diet, and exercise[463]. In addition, platelet-aggregation inhibition must be started. If low dose aspirin is not tolerated, clopidogrel must be used in stead. Statins must be used to reduce the total cholesterol to below 4.5 mmol/l – or even better - below 4.0 mmol/l, and Ldl must be reduced to below 2.5 mmol/l – or even better – below 2.0 mmol/l. The systemic blood pressure must be kept under 140/90 mmHg – or even better below 130/80 mmHg. These consequences are interesting, since they emphasise the need pharmacological intervention. Allmost all men having an AAA diagnosed by screening in Viborg County had borderline hypertension or manifest hypertension[16], and total-cholesterol levels above 4.0 mmol/l[436]. However, there are an increasing number of reports suggesting modern drugs for cardiovascular prevention may inhibit further aneurysmal progression, while others may stimulate further progression. Consequently, early detection of small AAA may not only provide an opportunity for general cardiovascular prevention, but also pharmacological inhibition of further progression of the AAA. If true, the cost effectiveness of screening for AAA could be improved because planned operations are the major area of screening costs [Study II]. In spite of data on this topic is not presented in Study VII, it seems very relevant to cover this potential in this thesis.

5.7.2.2. Potential pharmacological treatment

5.7.2.2.1. Platelet aggregation inhibitors

There has been an increasing interest in the role of the mural thrombus in AAA. Patients with AAA have a threefold higher median concentration of the complex between activated protein C and protein C inhibitor, which is a measure of thrombin generation than a control group. This may be due to local activation of coagulation[464]. The mural thrombus is reported to be metabolic active, and a potential source of proteases in AAA[465-468]. Moreover, the interface between the luminal side of the thrombus and the flowing blood is a site of constant thrombus renewal, which is linked to platelet aggregation-induced fibrin generation and neutrophile accumulation[469]. In view of these data, it has been hypothesized that platelet aggregation inhibitors could limit AAA progression. This hypothesis was initially explored in an experimental animal model, where exposure to abciximab [a potent platelet inhibitor] in rats with experimental AAA caused lower AAA expansion rates compared with controls[469].

Jean Baptiste Michel presented me for this hypothesis at an ECVR meeting in Nice. We did not describe the presence of a mural thrombus at our initial scan of our cohort of men with small AAAs, but the presence of a mural thrombus depends upon the size of the AAA, and we did register the use of low-dose aspirin. Consequently, he suggested that we should do subgroup analyses of our AAA cohort by dividing them into small [30-39 mm] or middle-sized [40-49 mm] AAA.

We found in cases sized 40-49 mm, a clear difference in crude expansion rates between low-dose aspirin users and non-users: 2.92 vs. 5.18 mm/year [difference 2.27 mm/year, 95% CI: 0.42; 4.11, P=0.017]. This difference persisted after controlling for smoking, educational level and co-morbidity [difference= 2.13, 95% CI: 0.58; 3.68, P=0.008]. The crude relative risk for later operative repair due to expansion for non-low-dose aspirin users with an AAA of 40-49 mm was 2.74 [95% C.I.: 1.06; 7.07]. This increased risk persisted after adjusting for smoking, educational level and co-morbidity [risk ratio: 2.75 [95% C.I.: 0.86; 8.77], but just failed to reach statistical significance. However, due to the nature of the study – an observational cohort study – residual confounding may be present. In addition, the number of middle-sized AAA is relatively small, and the risk of a chance finding is present[470]. Nevertheless, the results seem interesting because they bring a potentially new insight into the pathogenesis of AAAs and questions whether additional benefits can be achieved by more efficient platelet-aggregation inhibitors. However, the findings are controversial. Large observational cohorts, as the UK small AAA study, have not noticed this association but they apparently neither did a similar subgroup analysis. This will probably be done, and the results will be very interesting.

5.7.2.2.2. Statins

Statins have anti-inflammatory effects that could decrease the aneurismal expansion rate while wall concentrations of MMP9 - known to be associated with aneurysmal progression - are reported to be lower in statin-treated cases[471;472]. On the other hand, lipoprotein [a] inhibits the activation of plasminogen, and plasminogen seems to play a central role in the activation of the proteases involved in the aortic matrix degradation. Thus, lowering lipoprotein [a] could increase the aneurysmal expansion rate[473].

Recently, a retrospective study consisting of 59 statin users and 91 non-users with small AAAs kept under surveillance for a median period of 3.1 [1.1 – 13.1] years was presented. Multivariate analysis showed that statin users had a 1.16 mm/year lower AAA growth rate than non-users [95% CI 0.33 to 1.99 mm/year][409]. Unfortunately, the multivariate analysis did not adjust for smoking, which could introduce a serious risk of residual confounding. However, statin treatment of AAA patients as a general cardiovascular prevention seems justified in cases with coexisting cardiovascular morbidity, and after the findings in study VII justification seems to miss also in AAA patients without coexisting cardiovascular morbidity.

5.7.2.2.3. Antihypertensives

5.7.2.2.3.1. Beta-blockers

Fibrinogenetic reactions to beta-receptor blockage have been reported[474]. It has been hypothesised that beta-receptor adrenergic blockage with propranolol stimulates the lysyl cross-links in the synthesis of collagen[475]. A lifelong supply of propranolol in AAA-prone animals decreased the number and ruptures of AAAs[474;476-478].

A retrospective study of 27 human users of propranolol showed decreased expansion compared with 13 controls[442]. The tendency has been confirmed by others[479;480].

Three randomised trial have been performed. Firstly, we found[481] only 44% could attend the RCT because of present use of beta-blocker or contraindications, and 60% in the propranolol group and 25% in the placebo group dropped out. Furthermore, decreasing pulmonary function, decreasing ankle blood pressure index and decreasing QoL were noted in the propranolol group. Consequently, only 22% of small screening-diagnosed AAAs were treatable with propranolol for two years, and we consequently stopped the trial because of the side-effects and poor compliance. Later, the Huntingdon group presented similar results: poor compliance and no significant benefit [apparently never published]. In 2002, the Canadian large-scale multicentre study [N= 537] published similar results: poor compliance, decreased QoL among those in the propranolol group and similar mean growth rates in the two groups[482]. Finally, a large population-based case control study could not associate use of beta-blockers with reduced risk of being admitted to hospital due to ruptured AAA[483].

5.7.2.2.3.2. ACE inhibitors

Angiotensin converting enzyme [ACE] converts angiotensin I to active angiotensin II, and have been reported present in AAA-walls in abnormal high amounts[484]. Animal studies have shown that infusion of Angiotensin II is associated with development of large AAA[485]. In addition, studies on apolipoprotein-E-deficient mice have shown that inhibiting angiotensin II type 1 receptors with losartan totally prevents the formation of aneurysms. Similarly, losartan has proven capable of preventing aortic aneurysm in a mouse model of Marfan's syndrome, probably through prevention of excess TGFβ signalling[485-488]. In humans, angiotensin inhibitors have been associated with increases in collagen type III metabolism, a marker of collagen neosynthesis, which could compensate for loss of elastin and consequently stabilise an established AAA[489;490]. Consequently, high local levels of angiotensin II may play a significant role in the AAA pathogenesis. A polymorphic site in the ACE gene has been investigated; Fatini et al. compared the genotypes in 250 patients with AAA and 250 age and sex matched controls, and found a highly increased frequency of the D allele in AAA patients[491]. The findings were confirmed by Pola et al[492].

In a Canadian population-based case-control study of 15,326 patients above 65 admitted to hospital with intact or ruptured AAA, patients who received ACE inhibitors before admission were significantly less likely to present with ruptured aneurysms [OR=0.82 [95 % C.I.:0.74; 0.90]] than those who did not receive ACE inhibitors. [483]. Unfortunately, they did not include

deaths outside hospital due to rupture. Only 33-50% of ruptured cases reach hospital. If use of ACE-inhibitors changes the chance of reaching hospital due to for instance poorer compensatory capabilities, a serious selection bias would be present. However, overall, the results points to a beneficial effect on the natural history of AAAs. Most AAA patients have borderline or manifest hypertension. The traditional medical treatment for this condition has been diuretics, beta-blockers or calcium antagonists. It could be questioned whether ACE inhibitors ought to be the first drug of choice. In addition, ACE inhibition of AAA patients unfit for surgery could be considered.

5.7.2.2.3.3. Calcium channel antagonists

In 1990, Cohen and his coworkers found that neutrophils secrete more elastase in response to a calcium stimulus in AAA patients compared to patients with aortic occlusive disease, and that Verapamil, a Calcium channel antagonist, blocks elastase secretion ineffectively in AAA patients. They concluded that Verapamil is a poor drug to use to medically manipulate the protease system in AAA patients[493]. Later, animal studies suggested elastase promotes aortic dilation by inhibiting Ca2+ influx into vascular smooth muscle. In addition, data from 438 cases with an AAA >29 mm detected by population screening and 5373 controls have showed that use of calcium-channel blockers was independently associated with increased aortic stiffness and the risk of having an AAA after adjusting for relevant confounders [OR: 2.6 [95 % C.I.:1.5-4.2]. Other antihypertensive drugs showed no increased risk[490]. There seems not to be any reports of increased expansion rates among users of calcium channel blockers or increased risk of rupture but taken into consideration the presence of other efficient antihypertensive drugs, calcium channel blockers should perhaps not be the first drug of choice in AAA patients.

5.7.2.2.4. Antiinflammatory drugs

5.7.2.2.4.1. Tetracyclines or macrolides

As mentioned, antibodies against C. pneumoniae are associated with the clinical course of small AAAs, and C. pneumoniae-specific DNA has been detected in AAAs[280]. Consequently, 3 randomised, double-blinded controlled intervention trials have been performed.

The largest trial only found a transient benefit[280;292], while a sustained benefit was observed after a year in the second trial. The two trials had different treatment periods, and there seems to be no agreement about the duration of treatment in complicated cases of chlamydial infection. None of the trials have reported long-term results, which would otherwise be most relevant.

5.7.2.2.4.2. Non steroid anti-inflammatory drugs

Prostaglandin E2, other inflammatory mediators and proteases are produced in high quantities in the aneurysmal wall. By applying indomethacin to AAA cultures and analysing the media for collagen breakdown, MMP, and prostaglandin E2, Franklin et al.[494] showed that indomethacin reduced the amount of prostaglandin E2 and various interleukins. The findings suggested that indomethacin could control the inflammation in AAA walls by inhibiting cyclo-oxygenase-2 and, consequently, perhaps AAA growth. In a later small prospective cohort study they demonstrated that the mean AAA expansion rate was 1.5 mm per year in patients receiving NSAID, compared with 3.2 mm annually in non-NSAID users [$P<0.05$][495].

The above mentioned statin-study found no association between use of non-steroidal anti-inflammatory drugs and impaired AAA growth rate[409].

5.7.2.2.4.3. Steroid treatment

As mentioned, cysteine proteases, which seem to be involved in the aneurysmal degradation, are mainly inhibited by cystatin C. In vitro studies have shown that alveolar macrophages from cigarette smokers or monocytes stimulated by the inflammation mediating cytokine gamma-interferon secrete less cystatin C than unstimulated macrophages or monocytes. This suggests that cystatin C may be reduced in inflammatory areas causing less inhibition of cysteine proteases[268]. We have previously demonstrated a clinical effect of cystatin C in the form of a negative correlation between S-cystatin C and the progression of AAAs[271]. This finding suggests a potential role of steroid treatment, since in vitro studies have shown that administration of glucocorticoids increases the levels of cystatin C[271]. There are apparently no relevant clinical studies, and the value of observational studies could be limited by the strong association of steroid use and COPD.

PART VI. CONCLUSIONS AND FUTURE PERSPECTIVES

Although the number of elective operations for AAA [AAA] is increasing, the sex- and age-standardised mortality rate of ruptured AAAs continues to rise, especially among men aged 65 years or more. The lethality of ruptured AAA continues to be 80-95%, compared with 5-7% by elective surgery of symptom-free AAA. An asymptomatic phase with a relatively low-risk treatment, compared with the symptomatic phase, is a good recommendation for screening. However, all WHO, European, and national criteria for screening must be fulfilled[24-26].

Firstly, it seems that ultrasonographic screening is a suitable and acceptable method of screening. The acceptance rate was 77% in our study [I], and 95% accept control scans. Furthermore, studies of inappropriate selection have shown that persons at the

highest risk of having an AAA attend screening more frequently than persons at low risk [II]. The infrarenal aorta can be visualised in 98-100% of all cases, but the exact sensitivity and specificity of such screening remain unknown, but the estimated sensitivity is 98% and the estimated specificity 99%. The usual problems with respect to false positive and negative findings seem negligible because they will be revealed by the follow-up of small AAAs or by repeated [interval] screening [I].

Interval screening seems needed because the prevalence of AAA increases with age, and some of these new AAAs can then be recommended for surgery [I]. However, the amount of screening must be minimised because of the associated psychological and economic costs. We found [I] that 97% of the interval cases developed from aortas that initially measured 2.5-2.9 cm. Rescreening studies suggest that none of the newly found aneurysms were more than 5 cm in diameter after 3-5 years. Consequently, rescreening could be restricted to aortas initially measuring 2.5-2.9 cm, i.e. approx. 5% of the screened population, at five-year intervals [I].

There is always a risk that screening may lead to out-of-proportion fear and stigmatisation, with loss of quality of life. Consequently, one of the criteria for screening is that the disease must constitute a major health problem[24-26]. Today 1-3% of all deaths in men aged 65-80 years are related to AAA, and it is debatable whether this represents a major health problem. The offer of screening for AAA has caused similar, transient, mild reactions of fear, but repeated screening is only required in 5% of the initially negative findings, as mentioned above [I].

Furthermore, the indications for treatment need to be clear[24-26]. The size of the AAA is the only constantly mentioned prognostic indicator of rupture. The UK Small Aneurysm Trial and the similar ADAM study in the US both randomised more than 1000 AAAs, 4.0-5.5 cm in size, to early surgery or watchful waiting. No differences in AAA-related mortality were noticed between the two management strategies in the studies after five years. Consequnetly, 5.5 cm is used as cut point today. Furthermore, treatment must be acceptable[24-26]. Survivors of surgery have the same quality of life as the general population of the same age, and it seems that only 2-5% of patients refuse an offer of surgery. However, about 15% or more have contraindications for surgery, and 85-90% of the AAAs diagnosed at screening were initially too small to be recommended for operation [I]. Follow-up without surgery decreases the patient's quality of life. However, one third to half of these patients will undergo surgery within five to ten years [I,II] and early detection seems relevant since the cardiovascular mortality is more than four times higher in AAA patients without previous hospital discharge diagnoses due to cardiovascular disease than among similar men without AAA. The absolute risk difference after 5 years was 16%.

Consequently, they are very likely to benefit from general cardiovascular preventive action [VII]. In addition, general cardiovascular prevention strategies like smoking cessation [V], statin treatment and low-dose aspirin seem to be potential inhibitors of further AAA progression[VII].

Such developments would make early detection of AAA patients relevant, and would probably reduce the psychological side-effects because a treatment can be offered, but prolonged intervals between control scans could probably also reduce the side effects. Finally, the benefits of screening must outweigh the costs[24-26]. All four randomised trials presented in the present thesis point in the same direction, viz. in favour of screening of men aged 65 and above. The large MASS trial in the UK have reported 42% lower mortality of AAA by screening for £28,400 per saved living year equivalent to about £36,000 per quality-adjusted life year. They predicted the costs to be £8000 per life year gained after 10 years. Similary, screening significantly reduced AAA-related mortality by 67% in Viborg County within the first five years [I]. The number needed to screen to save one life was 352.

Little has been done to analyse the possibilities for further restricting the offer of screening to groups with even higher risk than based on gender and age. We found [II] that restriction of screening to men with previous cardiovascular or pulmonary hospital discharge diagnoses would request only 27% of the relevant male population study to be invited to screening, but would only have prevented 46.7% of the AAA-related deaths observed in the randomised mass screening trial after seven years of follow-up. The relative risk reduction by screening was similar in the high-risk and low-risk groups after 7 years, but low risk screening proved to gain the largest benefit by reducing AAA deaths by 78% after 14 years.[II,III].

In 2005, a systematic review and meta-analysis was made for the American preventive task force. Their metaanalysis of the RCTS showed that the offer of screening significantly reduced AAA-related mortality by 43%. Shortly after, the American preventive task force, working for the American government, recommended screening 65-year-old men who currently or ever smoked. Early in 2006, the British National Screening Committee also recommended screening of 65-year-old men. Consequently, several regions and countries are considering screening for AAA. However, the Chichester Aneurysms Screening Trial reported poor long-term benefit. Despite attractive sustained benefit and improved cost effectiveness was reported by MASS trial after 10 years, cost effectiveness of screening for AAA continues to be discussed [205;408;496-498]. We therefore supplemented previously published data with an analysis of the long term 14-year mortality from AAA and cost effectiveness of screening for AAA. After a mean observation time of 13 years, the offer of screening had reduced AAA-specific mortality by 66%. Consequently, the number needed to screen to save one life was just 135 after 14 years and the frequency of emergency operations due to rupture was significantly reduced by 56%. The cost per life year gained could be calculated at 157€ [1,170DKK] and the cost per QALY at 178€ [1,326 DKK] based upon all cause mortality[III].

The MASS trial reported after seven years of follow up the costs to be $19,500 [DKK 106,275] per life-year gained based on AAA-related mortality and $7600 [DKK41,420] per life-year gained based on all-cause death, and after ten years £7600 [DKK 66,500] per life year gained. Allthough, the ICER is not directly comparable, it points to that screening for AAA is cost effective in UK and Denmark. Consequently, the offer of screening to men in the high risk group seems acceptable based upon attendance rate and benefit of screening [II]. Whether it should be limited to this group is more doubtful, since screening decreased AAA related mortality equally among men with and without AAA-associated diseases [78% and 76%, respectively]. The ARR was approx. twice as high in the high risk group with 95 numbers needed to screen in order to prevent one death compared to 220 in the low risk group. However, 220 needed to screen to save one life is also quite low. After 14 years, high risk screening depressed the effect of screening to a risk reduction of 58% for of 385€ saved per life year less gained whereas low risk screening increased the relative risk reduction to 71% for 182€ per life year gained. Thus, low risk screening for AAA was cost effective in this trial. Similarly, subgroup analysis of only 65 year old men showed a similar benfit of reducing AAA mortality by 64% for 1,308€ per life year gained.

In all, the ethical dilemma of the prophylactic operation, the limited psychological side effects and minor uncertainties in the indications for treatment seem not to outweigh the benefits of screening. The results from I and II also show that the earlier planned detailed description[63] concerning organisation, management and administration, system to record relevant data, e.g. to ensure follow-up, plan for further referral and order of priority of positive findings, information to the target group, education and training of personnel, and execution of the test result, have worked satisfactory on the long term.

In all, we found that offering men aged 65-73 years screening for AAA seems acceptable according to criteria from WHO, Council of Europe, and the Danish National Board of Health [I,II,III].

In US, screening has been recommended since 2004, in UK, a national programme in UK is being implemented, a majority of the Swedish counties are implementing it[499] – recommended by a HTA, and programmes are about to start in Norway and Spain. In Denmark, a flawed HTA from the region of Mid Denmark based upon an economic model, which excluded large AAAs, emergency operations of unruptured cases, and costs for intensive care beyond 48 hours are blocking a qualified decision[316;408;500]. However, recent and yet not published publications[409;483] suggest that we are standing at the edge of a medical breakthrough in managing AAA too small to warrant recommendation of surgery; simple general cardiovascular prevention in the form of smoking cessation [V], statin treatment and low-dose aspirin seems to be able to increase AAA patients' remaining living years and to be potential inhibitors of further AAA progression and need for later AAA repair; preventive actions that were not taken in the present four randomised screening trials.

The increasing health problem with AAA and the accumulating evidence in favour of screening for AAA have probably stimulated the European Commision to ask for major grant applications for aneurysmal research, and a European network of AAA-researchers including Danish researchers have given a major grant in 2008.

Interesting topics for the future will be analysing the benefits and costs of adding ankle-brachial systolic blood pressure measurements to AAA-screening programs, since impaired ankle blood pressures is strongly associated to low survival, it can be measured non-invasively within few minutes, and efficient preventive actions are present. Other interesting topics would be development of predictive models of expansion and rupture, establishment of proper indications for EVAR and solid registry based observational studies on the association between AAA and existing drugs used in cardiovascular medicine, followed by pharmacological randomised trials of relevant identified drugs to prevent AAA progression.

Multivariate predictive models involving the most promising predictors must be created and validated.

We found AAA-size, wall calcification, smoking, tPA and antibodies against C. pneumoniae to be such candidates [IV,V].

Other candidates would especially be elastin peptides, if a standardised ELISA can be developed, or perhaps Desmosine.

More precise methods for measuring the degree of wall calcification must be developed and validated. The mechanisms behind the role of calcification must be studied through finite element analysis to search for mechanical explanations and proteomic research to search for biochemical explanations.

Randomised controlled trials with low-dose aspirin and statins seem not ethically acceptable due to the relatively high cardiovascular mortality among AAA patients, and such prevention must be considered in all AAA-patients[VII], but in an effort to inhibit AAA growth and to reduce the need for later AAA repair and the associated mortality, more potent platelet-aggregation inhibiting drugs should be compared with low-dose aspirin, and ACE inhibitors should be compared with controls in randomised trials on an intention to treat basis and including AAA deaths outside hospitals. Later, testing of low-dose steroid treatment and low-risk non-steroid anti-inflammatory agents could be relevant.

Chlamydial infection has for a long time been strongly suspected to be involved in the progression of AAA. However, the results of antibiotic treatment trials are disappointing, and recently we demonstrated no sign of C. pneumoniae in AAA walls but rather signs of proteins cross-reacting with chlamydial antibodies indicating "molecular mimicry" as an autoimmune reaction [VI].

This observation supports the relevance of testing anti-inflammatory drugs as inhibitors of aneurismal growth.

SUMMARY

Although the number of elective operations for AAA is increasing, the sex- and age-standardised mortality rate of AAAs continues to rise, especially among men aged 65 years or more. The lethality of ruptured AAA continues to be 80-95%, compared with 5-7% by elective surgery of symptom-free AAA. In order to fulfil all WHO, European, and Danish criteria for screening, a randomised hospitalbased screening trial of 12,639 65-73 year old men in Viborg County (Denmark) was initiated in 1994.

It seemed that US screening is a valid, suitable and acceptable method of screening. The acceptance rate was 77%, and 95% accept control scans. Furthermore, persons at the highest risk of having an AAA attend screening more frequently. We found that 97% of the interval cases developed from aortas that initially measured 2.5-2.9 cm - i.e. approx. only 5% attenders need re-screening at 5-year intervals.

Two large RCTs have given clear indications of operation. Survivors of surgery enjoy the same QoL of life as the background population, and only 2-5% of patients refuse an offer of surgery.

Early detection seems relevant since the cardiovascular mortality is more than 4 times higher in AAA patients without previous hospital discharge diagnoses due to cardiovascular disease than among similar men without AAA. The absolute risk difference after 5 years was 16%. So, they will benefit from general cardiovascular preventive action as smoking cessation , statins and low-dose aspirin, which could inhibit further AAA progression.

All 4 existing RCTs point in the same direction, viz. in favour of screening of men aged 65 and above. We found that screening significantly reduced AAA-related mortality by 67% within the first five years (NNT=352). Restriction of screening to men with previous cardiovascular or pulmonary hospital discharge diagnoses would request only 27% of the relevant male population study to be invited, but would only have prevented 46.7% of the AAA-related deaths. However, the benefit was similar, and low risk screening reduced AAA specific mortality by 78% compared to 52% in the high risk group after 14 years.

Despite attractive sustained benefit and improved cost effectiveness was reported by MASS trial after 10 years, cost effectiveness continues to be discussed. We found after 14 years that screening had reduced AAA-specific mortality by 66% (NNT=135). The cost per life year gained was 157€ [1,170 DKK] and the cost per QALY at 178€ [1,326 DKK].

In all, the ethical dilemma of the prophylactic operation, and the limited psychological side effects seem not to outweigh the benefits of screening. Conclusively, we found that offering men aged 65-73 years screening for AAA seems acceptable according to criteria from WHO, Council of Europe, and the Danish National Board of Health .

In US, UK, and Sweden national programmes are implemented. In Denmark, a flawed HTA from the region of Mid Denmark based upon an economic model, which excluded large AAAs, emergency operations of unruptured cases, and costs for intensive care beyond 48 hours are blocking a qualified decision.

Future topics for will be creation and validation of multivariate models predicting need for later repair. We found AAA-size, wall calcification, smoking, tPA and antibodies against *C. pneumoniae* to be such candidates. Antibiotic treatment for chlamydial infection are disappointing, and we found no sign of C. pneumoniae in AAA walls but rather signs of proteins cross-reacting with chlamydial antibodies indicating "molecular mimicry" as an autoimmune reaction, which calls for further attention. .

More precise methods for measuring the degree of wall calcification must be developed and validated.

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