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Screening for Abdominal Aortic Aneurysm

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1. Introduction

A fast-growing body of literature is providing evidence in favor of screening men for abdominal aortic aneurysm (AAA). Several large, randomized trials published in the past few years have consistently shown that screening reduces AAA-related mortality.[18]

2. Cost-effectiveness of screening

Longer-term mortality benefit and cost-effectiveness for abdominal aortic aneurysm (AAA) screening are uncertain.[18]
In addition to the mortality benefit, evidence indicating that screening is highly cost-effective is increasing.[2, 34] In light of this evidence, national screening programs are now being considered in many countries.[47, 46]
However, there is little evidence regarding long-term outcomes after AAA screening; almost all of the evidence from randomized trials is limited to the first 4 years after screening.[18]
It is therefore expected that cost-effectiveness of screening will improve over time.[18]
It is expected that the lifetime cost-effectiveness of screening will be highly favorable. Furthermore, these results show that the mortality benefit of an approximate 50% reduction in AAA-related death in patients invited to be screened is maintained at 7-year follow-up. The risk for AAA rupture remains low in patients with normal results on initial screening.[18]
Patients with AAA detected in selective screening at the vascular laboratory had a high level of morbidity and inferior long-term survival when compared with the general population. Elective AAA repair rate was lower in this group than in patients with AAA detected in general screening programmes, with an acceptable perioperative mortality rate. Despite these factors, selective screening for AAA among patients referred to the vascular laboratory for suspected arterial disease was cost-effective under most assumptions with an estimated ICER at base-case of 11 084 Euro/LYG compared with non-screening.[28]
Screening appears to reduce hospital AAA mortality and to be cost-effective.[25]
The benefit of inviting men aged 65-74 to screening for abdominal aortic aneurysm continues at about the same rate 7-10 years after screening, as observed in previous years. The reduction in number of deaths related to abdominal aortic aneurysm in MASS is estimated as 42% at four years[34], 47% at seven years[18], and now 48% at 10 years. This is surprising as it might be expected that ruptures of the aneurysm in those originally screened as normal and incidental detection of abdominal aortic aneurysm in the control group would erode the benefit over time.[45]

A crucial problem is the extent to which those screened as normal will go on to develop an aneurysm that ruptures and whether rescreening of participants after a normal scan is justified at any stage.[45]

Women are generally not considered a suitable target population for abdominal aortic aneurysm (AAA) screening. The main reason is not only the low prevalence of AAA but also a development of the disease later in life and an inferior relative long-term survival in women with AAA. However, other aspects of the disease, such as the higher rupture rate, indicate that AAA in women may be more severe than in men. Screening reduced the AAA rupture incidence by 33% and the AAA-related death rate by 35%. The cost per life year gained was estimated at $5911. The incremental cost-effectiveness ratio was similar to that found for screening men, which reflects the fact that the lower AAA prevalence in women is balanced by a higher rupture rate. Screening women for AAA may be cost-effective, and future evaluations on screening for AAA should include women.[50]

Cost-effectiveness was rather insensitive to variations in prevalence >1%. Below this level, however, the cost per life year gained increased rapidly.[50]

The rupture rate has a large impact on the cost-effectiveness of a screening program,10 and the higher rupture rate among women compensates for the lower prevalence and reduces the cost per life year saved by 64%.[49]

The sensitivity analysis showed, however, that the incremental cost per life year gained was lower than what is generally considered cost-effective, even if the rupture rate among women with AAA was assumed to be the same as for men.[50]

The life expectancy of the screened individuals is a key variable for the cost-effectiveness ratio.[49]

The incremental cost per life year gained for screening all 65-year-old women for AAA was lower than what is generally considered cost-effectiveand was similar to that for screening men at the same age.This reflects the fact that in women, a low prevalence is balanced by a high rupture rate.[50]

3. Treatment decisions

The major problem with AAAs is the risk of rupture. AAA is often asymptomatic and if left undetected they will continue to expand and may eventually rupture.[11]

Decisions about the treatment of AAAs are traditionally based upon the maximum cross-sectional diameter. If the AAA diameter is 5.5 cm or larger then intervention is generally deemed appropriate.[11] The diameter of an AAA is a well established objective criterion for selecting patients for treatment and when assessing the results following endovascular repair.[11]

New treatments for abdominal aortic aneurysm may impact on a national screening programme and increase its effectiveness. Endovascular repair of aneurysms rather than conventional open repair is now used more widely for elective surgery but was used for only 9% of the elective procedures in MASS. In patients who are fit for open repair, and anatomically suitable for endovascular repair, endovascular repair has lower operative mortality than open repair and fewer deaths related to abdominal aortic aneurysm in the longer term[10, 12, 13, 21]; it may therefore be preferred by both patients and surgeons. Reliable evidence comparing endovascular repair of abdominal aortic aneurysms with open repair is currently available only up to four years of follow-up; it shows no difference in all cause

mortality[21] but a substantial incidence of graft problems (for example, leaks around the graft or movement of the graft) and need for reinterventions after endovascular repair.[13, 10]
The quality of life data collected in the trial around the time of screening showed no clear adverse or beneficial effects of screening or any long term effects after surgery.[34, 29]
Patients with a detected AAA have yearly revisits to follow the expansion of the aneurysm. They are offered elective open surgery, if they are healthy enough, when the AAA has grown to >55 mm, has expanded rapidly, or has caused symptoms. Some patients with detected AAA fulfill the criteria for elective surgery at the time of screening and will be offered surgery as soon as possible.[50]

4. Age and screening

The prevalence also depends on the age of the screened population. However, the present lack of age-specific prevalence data in women makes a more precise analysis of the optimal screening age difficult.[50]
The results suggest that aortic screening may be worthwhile extending to a wider age band. By focusing follow-up, this should give greater value for younger men in terms of community productivity and allows for selective intervention in the elderly.[32]
The United States Preventative Services Task Force (USPSTF) recommends one-time screening for AAAs in men 65 to 75 years of age who have ever smoked and recommends against routine screening in women, and the Screening Abdominal Aortic Aneurysms Very Efficiently Act supports only a screening program for AAA in male ever- smokers when they turn 65 years old.[5]
The mortality benefit of screening men aged 65-74 for abdominal aortic aneurysm is maintained up to 10 years and cost effectiveness becomes more favourable over time. To maximise the benefit from a screening programme, emphasis should be placed on achieving a high initial rate of attendance and good adherence to clinical follow-up, preventing delays in undertaking surgery, and maintaining a low operative mortality after elective surgery. On the basis of current evidence, rescreening of those originally screened as normal is not justified.[45]
The reduced benefit of screening elderly males is due to the reduced life expectancy and to the demonstrated increased mortality after AAA repair.[30]

5. Sex and screening

Among men, the rupture risk of an AAA was estimated at 0.8% per year among those with an AAA attending a screening and 1.9% among those with an AAA not attending a screening or not invited to a screening.[49] Women were estimated to have a threefold higher rupture risk than men.[37] Thus, the corresponding annual rupture risks were 2.4% and 5.7%, respectively, for women with AAA. Sixty-five percent of men with ruptured AAA die before surgery, and an additional 14% die during surgery, corresponding to an operative mortality of 40%.[49]The rate of surgery for ruptured AAA was lower for women[50] and the operative mortality was higher. Thus, the total mortality for AAA rupture was estimated at 86.3% for women compared with 79% for men.[50]
The Chichester screening trial is the only published evaluation of screening for AAA in women. Some 9342 women aged 65 to 80 years (mean age, 72 years) were randomized, with no difference in rupture rate between the screened and the control groups after 10 years

follow-up. The authors concluded that it was neither clinically indicated nor economically rational to screen women.[40] However, a possible limitation that is likely to counteract the possible benefits of screening women is the biased mortality data based on official statistics. With a low autopsy rate, the reliability is limited in determining mortality rate from ruptured AAA. The autopsy rate has decreased to an overall 11% in Sweden, and is almost nonexistent among women >80 years old.[1]

Among 2257 AAA patients enrolled in the UK Small Aneurysm Trial (UKSAT) or Small Aneurysm Study, the risk of rupture was, independently of age and initial AAA diameter, associated with female sex. The rupture rate was three times higher in women compared with men. [37]

Only one RCT, the Chichester trial, included women (n = 9342) aged 65–80 years old. In this trial, the prevalence of AAA >3 cm among women (1.3%) was substantially lower than in men (7.6%). The subgroup analysis addressing the effect of screening in women concluded that screening followed by surgery did not reduce mortality.[41]

In women, the incidence of ruptured AAA was similar in the control and screening groups, and in general the incidence of death from ruptured aneurysm increased with age, since more than 70% of ruptures occurred among women > 80 years.[41]

On the basis of the low prevalence of AAA in women and the unfavorable RR, screening of women may not be beneficial or cost effective.[41]

The evidence available from the Chichester trial regarding the effect of population screening in women should be considered with caution because of the possibility of confounding factors or biases. The gender analysis was a subgroup analysis and, as expected, the number of participating women was considerably lower than men. Since the risk factors associated with increased risk for surgery are the same as those associated with increased incidence of AAAs, it is possible that many women were excluded, giving a falsely lower incidence of AAAs (ascertainment bias).[5]

Before making a final decision on the effectiveness of AAA screening in women, a number of features unique to women should be considered. The lower prevalence of AAA in women is most likely due to their lower burden of risk factors compared with men. The evidence supports that like in men, for women the probability of AAAs is increased among smokers (odds ratio (OR) 3.8), those aged >70 years (OR 1.8), family history (OR 2.6), and pre-existing cerebrovascular disease (OR 3.20).[20]

Like coronary heart disease, the increase in prevalence of AAA among women appears to occur approximately one decade after men. Because of this 10-year delay in onset, and lower burden of AAAs likely due to the currently more favorable cardiovascular risk factor profile of women, the cost effectiveness of screening and repair of AAA to prevent death does not favor screening at present.[5]

However, we must also consider the observation that although women have a lower incidence of AAA, when they are found to have an AAA > 3 cm the risk of rupture is greater than that of men, [33, 6] and mortality associated with surgery for ruptured aortic aneurysms is higher compared with that in men.[41]

This higher risk of rupture in women may be because the prevalence of the disease was defined as an aorta with a diameter >3 cm, which is the usual threshold used for men, and it does not take into account the smaller size of a normal aorta in women. Thus, an aneurysm of 5 cm in a woman may have a higher rupture rate because it is equivalent to an aneurysm of 6 cm in a man. Given the state of the evidence, a number of outstanding issues should be

considered for the screening of AAA in women. First, the evidence does not support population-based screening over 65 years of age, due to the low incidence of AAA. However, it would be reasonable to recommend targeted screening of 'higher risk women', including those of an older age, who are current or had a long history of smoking, as well as those with co-existing vascular disease.[5]

In men, an AAA diameter of 55 mm generally justifies elective repair, whereas it has been suggested that women may benefit from a lower threshold for surgery. A lower threshold diameter for surgical repair in women (≤50 mm) may reduce the difference in surgery rate and the likelihood of an AAA to rupture. In the UKSAT, the mean AAA diameter at rupture was 50 mm for women and 60 mm for men. They concluded that different thresholds should apply to women than men when AAA repair is being considered.[37] In the Chichester trial, however, a threshold diameter of 60 mm did not result in higher rupture rate.[40]

The relative long-term survival after surgery for AAA was found to be better in men than in women, although the crude long-term survival was similar between men and women, because women in general have a longer life expectancy. The assumed additional relative mortality in women with AAA compared with men increased the cost per life years saved by 30%.[50]

the decrease in AAA-specific mortality among women invited to screening was only 32% compared with 50% among men. The explanation lies in the complex relations between mortality, risk of rupture, and risk of elective surgery. If women had an identical compliance and rupture rate as men, the model would generate a decrease in AAA-specific mortality of 43%.[50]

6. Size of aneurysm

Within group of detected aneurysms, surveillance involved rescanning: annually for those with diameters of 3.0-4.4 cm and every three months for those of 4.5-5.4 cm. Patients were referred to a hospital outpatient clinic for possible elective surgery when the aneurysm reached 5.5 cm, the aneurysm had expanded by 1.0 cm or more in one year, or symptoms attributable to the aneurysm were reported.[45]

The prevalence of the disease is, however, highly dependent on the definition used.[26] In most population-based screening studies including women, an AAA was defined as the maximum infrarenal aortic diameter being ≥30 mm, as proposed by McGregor.[31] Because the normal aortic diameter differs by gender,[44] a fixed diameter may not be an optimal definition of AAA and may partly explain the differences seen in prevalence between men and women.

In the Chichester trial, four of the 10 women from the screened group who had AAA rupture or emergency repair initially had a normal scan.[40] This may be the result of how an AAA was defined, where a fixed diameter may result in false-negative findings, or a consequence of the natural history of AAA development among women.

7. Rescreening

Two of the RCTs looked at the need for rescreening in individuals with <3 cm AAA: the Viborg trial repeated an ultrasound examination (USE) 3 to 5 years after the first one and found that new AAA > 3 cm occurred in 28% (95% CI 21-35), but none were clinically

significant (the largest <48 mm); and the Chichester trial rescreened patients with aortic diameter <3 cm every 2 years and identified 4.1% AAA, which were all <3.8 cm in diameter.[30]

Recommending rescreening those with an initial normal scan would only become justified in subsequent years if future analyses show that there is a further noticeable increase in ruptures in this group that is not sufficiently offset by the reduction in number of deaths related to abdominal aortic aneurysm for those with an aneurysm detected (or rendered unimportant by the overall toll of mortality from all causes).[45]

8. Psychological effects of screening

The offer of screening causes transient psychological stress in subjects found not to have AAA. However, diagnosis of an AAA seems to impair QL permanently and progressively in conservatively treated cases. This impairment seems reversible by operation. Nevertheless, the impairment seems considerable, and must be considered in the management of AAA and in the final evaluation of screening for AAA. [26]

Several concerns have been raised about the utility of population-based screening for AAA. It has been proposed that patients who are found to have "small" aneurysms will experience a diminished quality of life related to concern about rupture.[17]

For strategies toward other target groups, and management of small AAAs, prediction models and cost-effectiveness analyses are needed to provide guidance.[14]

9. Family history and screening

The ADAM study found that a family history positive for presence of AAA is associated with a two-fold increase in the risk of having an AAA with no difference between men and women.[30]

Familial AAA do not expand faster nor are they associated with unusual locations, but they may occur earlier in life. Screening causes psychological side effects, and it could therefore be offered to male first-degree relatives from the age of 60, and be confined to ultrasonographic scanning of the infrarenal abdominal aorta at five-year intervals. [23]

Aging brothers of patients with known abdominal aortic aneurysm have the highest risk for developing the disease; the prevalence of the disease in siblings older than 60 years of age is 18%.[39]

Ultrasonographic screening is recommended in brothers (50 years) of patients with aneurysms of the abdominal aorta.[4]

10. Screening methods

10.1 Physical examination

A focused physical examination has been investigated as a screening tool to identify AAA. Sensitivity has been reported in the range of 76% to 85% and specificity 85% for AAA >5 cm with moderate interobserver agreement (kappa = 0.5).31 The diagnostic properties of physical examination require further investigation.[30]

10.2 Ultrasonography

Ultrasonography is the detection method of choice for AAA screening: it is cheap and noninvasive and can be used easily in a community setting.[36]

Results from a large, pragmatic randomized trial show that the early mortality benefit of screening ultrasonography for AAA is maintained in the longer term and that the cost-effectiveness of screening improves over time.[18]

Ultrasound screening to identify abdominal aortic aneurysms (AAA) >5cm followed by surgery reduces cause-specific mortality among individuals older than 65 years. This benefit is not apparent among men older than 75 years, 5 and there is some controversy regarding the benefit of screening for AAA among women.[5]

The United Kingdom Multicentre Aneurysm Screening Study (MASS)[18,46] has provided most of the worldwide randomised evidence for the mortality benefit after ultrasound screening for abdominal aortic aneurysm.[8, 16] The UK screening programme for men aged 65 is based closely on the protocol and procedures in MASS. Some uncertainties relating to screening remain, however, including its long term benefit in terms of mortality and cost effectiveness, whether rescreening those with a previously normal scan is warranted, and the extent to which incidental detection of abdominal aortic aneurysm erodes the benefit of a systematic screening policy over time. It might be expected that the mortality benefit seen in the early years after one-off screening would decrease over time. MASS, started in 1997, runs more than 10 years ahead of the UK national screening programme and is uniquely positioned to tackle these uncertainties and to inform the development of the national programme.[45]

The neck of the aneurysm and suprarenal aorta might be more difficult to visualize with ultrasonography, and most ultrasound screening studies report only the maximum anterior-posterior diameter. However, ultrasonography also can provide information about the size and shape of the luminal thrombus in an AAA and the presence of iliac aneurysms.[36]

It is able to define the diameter of the infrarenal aorta in 98% (95% CI 92-94) of individuals, with a sensitivity and specificity of 100% and 98%, respectively. The correlation between observers for ultrasound measurements of the abdominal aorta is high (Spearman coefficient = 0.99), but abdominal girth reduces the precision of the measurement.[30]

Abdominal palpation has only moderate overall sensitivity for detecting AAA, but appears to be highly sensitive for diagnosis of AAAs large enough to warrant elective intervention in patients who do not have a large girth. Abdominal palpation has good sensitivity even in patients with a large girth if the aorta is palpable.[15]

Many large AAAs currently remain undetected until rupture, and many small AAAs that will never rupture are detected incidentally and repaired, with some resulting morbidity and mortality. Both scenarios contribute to aortic aneurysms remaining a leading cause of death. Recent randomized trials have demonstrated a substantial reduction in AAA-related mortality from ultrasonographic screening and resulting elective repair. If the U.S. Preventive Services Task Force recommends AAA screening, health plans, including Medicare, will probably follow with coverage and the era of AAA screening will begin. Meanwhile, it is reasonable to offer 1-time ultrasonographic screening to men 65 to 79 years of age who have ever smoked, especially if elective repair can be reserved for AAAs 5.5 cm or larger. If screening is accompanied by prudent use of elective repair, the mortality associated with AAA may at last be reduced. [19]

10.3 Computed tomography (CT) scan

The accuracy of radiographers in performing AAA CT measurements is encouraging. Variability exists for both professions, and in some instances may be clinically significant.

Observers should be aware of measurement variability issues and have an understanding of the factors responsible. Careful and repeat measurements of AAAs around 5.5 cm are recommended in order to define treatment.[11]
A good level of agreement exists between radiologists and radiographers in performing CT measurements of maximum AAA diameter. Variability for both professions does exist and can be significant in certain situations, observers should be aware of the existence of variability especially when making treatment decisions. It is technically feasible for radiographers to perform such measurements, whether this area of role extension should be explored needs further investigation. Understanding the factors which play a role in observer variability is paramount; variability may be decreased if using standardised measurement protocols, 3D techniques and computer-assisted measurements. If the latter is to be accepted then these measurements will require validation and clinical checking before prescribing treatment.[11]

10.4 Magnetic Resonance Images (MRI)

It seems that MRI screening of older men with LBP for AAA, especially in smokers or patients with a recent history of smoking, is advantageous. Further studies are needed to determine the best modality and the most feasible method of screening.[42]

10.5 Plasma levels of plasmin-antiplasmin-complexes

Three proteolytic systems seem involved in the aneurysmal degradation of the aortic wall. Plasmin is a common activator of the systems and could thus be predictive for the progression of abdominal aortic aneurysms (AAAs).[24]
The levels of elastase have been found elevated in the circulation and aneurysmal walls compared with those with aortic occlusive atherosclerosis.[3, 7, 9]Furthermore, circulating levels of Cystatin C B, the major inhibitor of cysteine proteases, have been reported decreased in aneurysmal cases compared with a sex-matched and age-matched control group.[43] Finally, the levels of various metallodependent proteases (MMPs), especially MMP2 and MMP9, have been found elevated in aneurysmal aortic walls compared with aortic walls of occlusive atherosclerosis[35, 38], and we have earlier reported a positive significant correlation between the plasma level of MMP9 and the expansion of small AAAs.[27]The progression of AAA is correlated with the PAP level, which seems to have a predictive value similar to the best serologic predictor known, serum-elastin-peptides.[24]

10.6 Genetic screening

Nine functional positional candidate genes on AAA1 locus on chromosome 19 were investigated. Two of the genes, *CD22* and *PEPD* showed modest level of evidence of being involved in AAA pathogenesis. This evidence came from a nominal association of SNPs residing in these genes to AAA, identification of novel sequence changes and expression of these proteins in aneurysmal tissue. If replicated in independent studies, the findings provide important information about AAA pathogenesis. Association testing of the functional positional candidate genes on the AAA1 locus on chromosome 19q13 demonstrated nominal association in three genes. *PEPD* and *CD22* were considered the most promising candidate genes for altering AAA risk, based on gene function, association evidence, gene expression, and protein expression. [22]

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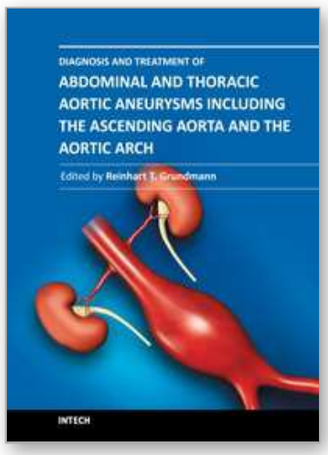

Diagnosis and Treatment of Abdominal and Thoracic Aortic Aneurysms Including the Ascending Aorta and the Aortic Arch
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This book considers diagnosis and treatment of abdominal and thoracic aortic aneurysms. It addresses vascular and cardiothoracic surgeons and interventional radiologists, but also anyone engaged in vascular medicine. The book focuses amongst other things on operations in the ascending aorta and the aortic arch. Surgical procedures in this area have received increasing attention in the last few years and have been subjected to several modifications. Especially the development of interventional radiological endovascular techniques that reduce the invasive nature of surgery as well as complication rates led to rapid advancements. Thoracoabdominal aortic aneurysm (TAAA) repair still remains a challenging operation since it necessitates extended exposure of the aorta and reimplantation of the vital aortic branches. Among possible postoperative complications, spinal cord injury (SCI) seems one of the most formidable morbidities. Strategies for TAAA repair and the best and most reasonable approach to prevent SCI after TAAA repair are presented.

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