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Review Article

Abdominal aortic aneurysm screening: are those at high-risk being overlooked?

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ABSTRACT

An abdominal aortic aneurysm (AAA) is defined as enlargement of an abdominal aorta with a diameter of 3.0 cm or larger in the anteroposterior or transverse plane. In order to diagnose and treat this disease early, clinical trials were conducted to evaluate the benefits of ultrasound screening for AAA. There is enough good evidence to recommend AAA population ultrasound scan screening for men over 65 years old. Prevalence rates for AAA amongst males at age 65 detected by screening appear to be decreasing, however AAA screening continues to be cost effective. There has been emerging evidence suggesting a strong link between family history and development of AAA. The prevalence of AAA amongst family members has been higher when compared to general population. This high prevalence of AAA in the first-degree relatives provide a strong argument for aggressive approach to screening of this specific cohort. After the latest literature review, there have been no data from a single randomised clinical trial or large nonrandomised studies published with 'targeted USS screening' with regards to family history of AAA. Ultrasound screening for the first-degree relatives, both male and female, of patients with AAA appears to be feasible and cost effective. A pilot study to determine the prevalence of familial AAA amongst probands and the prevalence amongst first degree relatives should identify the unmet need for AAA screening for this cohort and quantify the resources required for a sustainable screening programme.

Keywords: AAA prevalence, AAA screening, Familial AAA, Targeted screening

INTRODUCTION

An aneurysm is a permanent dilatation of an artery by at least 50% of the normal expected diameter of an artery.[1] An abdominal aortic aneurysm (AAA) is defined as enlargement of an abdominal aorta with a diameter of 3.0 cm or larger in the anteroposterior or transverse plane. The exact cause of AAA is unknown however AAAs are more commonly associated with atherosclerosis.[2] There are modifiable and non-modifiable risk factors contributing towards the development of AAA. Non-modifiable factors include age, sex, ethnicity and family history. Modifiable factors include hypertension, obesity, smoking, hypertriglyceridemia and low density lipoproteins.[3] Approximately 4000-6000 deaths per year occur from the condition in England and Wales, primarily in men over 65 years of age.[4] In order to diagnose and treat this disease early, clinical trials were conducted to evaluate the benefits of ultrasound screening for AAA.

SCREENING FOR AAA

There have been four important population-based large Randomised Controlled Trials (RCT) in the literature comparing AAA screening in asymptomatic men over 65 with routine care. The largest trial was the Multicentre Aneurysm Screening Study (MASS) started in 1997, which randomised asymptomatic men between 65 and 74

years to a screening ultrasound scan (USS) or a control group receiving standard care.[5] This revealed that a single ultrasound scan in that cohort significantly reduced the aneurysm-related mortality by 53% with absolute risk of 0.33% and was demonstrated to be cost effective in long term.[6]

The Chichester study (1995), commencing prior to the MASS trial, randomised asymptomatic men between 65 and 80 years of age to AAA USS screening compared to a control group. It had longer follow up (up to 15 years) and showed similar findings to the MASS trial.[7] The original screening programme of the Chichester study recruited asymptomatic women between 65 and 80 years of age as well, but it did not show any additional advantage or reduction in AAA-related deaths in women; in fact it concluded that screening in women is not clinically indicated and it is not cost effective.[8,9]

The Danish trial (2005) with a population of asymptomatic men in the 64-73 year age group concluded findings consistent with the MASS trial.[10] Interestingly, an Australian study (2004) enlisting 65-83-year-old asymptomatic men for AAA screening, did not show any additional benefits in terms of AAA-related mortality from the screening, probably due to decreased smoking incidence among the cohort.[11] However, sub-analysis of 65-74 years-old males had shown some benefit in reduction of mortality from AAA rupture. Clinical practice in Australia is different to the United Kingdom (UK). Australian general practitioners had direct access to request imaging such as computed tomography (CT) probably resulting in more incidental and earlier diagnosis of AAA as compared to the UK health system.

The prevalence of AAA across the globe from these four major studies varies between 4% and 7.6%. The Danish study found a prevalence of 4% in their trial of asymptomatic men of 64-73 years age group whereas, the Western Australia trial had 7.2% in asymptomatic men of 65-83 years age group.[12,13] The United Kingdom (UK) populations studies, Multicentre Aneurysm Screening Study (MASS) and the Chichester study, showed the prevalence of AAA as 4.9% and 7.6% respectively.[5,8] The Cochrane review publicised the evidence from the four population based randomised trials concluding that screening in men, decreases mortality of AAA by almost half [odds ratio (OR) 0.60, 95% confidence interval (CI) 0.47 to 0.78]. This formed the basis for AAA screening in elderly men between 65 and 75 years old in the United States of America (USA).[14]

The national AAA screening programme (NAAASP) has been widely implemented across the UK since 2009 in different phases. The programme uses ultrasonography, which is inexpensive, easily available, non-invasive, safe and efficient with high specificity and sensitivity as a screening tool to determine the size of abdominal aortic aneurysms to reduce the overall morbidity and mortality.[15] The risk of rupture increases with the size. AAAs with diameters of 3.0 to 3.9 cm have a nearly 0% annual rupture risk, AAAs between 4.0 and 4.9 cm have a 1% risk, and the risk increases to 11% for AAAs between 5.0 and 5.9 cm.[16]

The prevalence of AAA in the UK asymptomatic male population between 65-74 years age group is around 1.34% from NAAASP, lower than the expected rate of 4.9% recorded in the randomised trials of two decades ago.[17] It has decreased to 1.7% and 3.3% in other European countries like Sweden and Denmark respectively.[18,19] This decline in the rate may be due to lifestyle modifications including smoking reduction and a wide availability of Statin medications.[20] Within the UK, the highest incidence of AAA is among white-British as compared to non-British.[21]

The invitation of screening for AAA could cause unnecessary 'transient psychological stress' in patients who may not have the condition. Moreover, a confirmed diagnosis of AAA in patients who do not undergo surgical treatment may perpetually weaken the quality of life score.[22] Screening also detects asymptomatic AAA requiring elective repair, which adds to increased morbidity and mortality in patients who subsequently undergo elective repair. However, randomised trials of population-based screening for AAAs with abdominal ultrasound showed that screening for AAA significantly reduces the risk of AAA-related mortality by approximately 50% in men older than 65 years of age. [15] It also reported significant reduction (89%) in AAA-related deaths in smoker men between 65 and 74 years of age. The NAAASP still remains cost effective for men over 65 years of age at the current prevalence of 1.3% and should continue to be cost effective unless prevalence drops to less than 0.35%. There is enough good evidence to recommend AAA population USS screening for men over 65 years old.[23]

SCREENING IN WOMEN

Screening in women seems to be controversial. Men are almost six times more likely to develop a AAA than women.[9] The overall prevalence of AAA in women between the ages of 65-80 years, from the Chichester study with the largest number of women, was 1.3% compared with 7.6% in men.[9] Interestingly, the study found the size of AAA in women at the time of diagnosis was smaller and the mortality related to the disease occurred mostly after 80 years of age. A recent meta-analysis of 8 studies of women 60 years of age or older concluded that the overall prevalence of AAA in women ranges from 0.37% to 1.53%.[24] This increases with age from 0.43% in those between 61 and 70 years, to 1.15% in those between 71 and 80 years, and to 1.68% in those over the age of 80 years. The overall pooled prevalence of AAA in women over 60 years old was 0.7%. Currently, population screening in women for AAA is not recommended by the European society for vascular

surgery (ESVS) based on the evidence available so far (Class III, level B).[23]

The current definition of an AAA-'maximum infrarenal aortic diameter >3 cm on USS, an approximately 50% increase in normal infrarenal aortic diameter'-is mainly derived from studies that predominantly included men. The Framingham heart study in Caucasians established the median diameter of the infrarenal aorta in men over 65 year is 2·02 cm, whereas in women of same age group, the median infrarenal aortic diameter is only 1.75 cm.[25] These findings prompt a discussion to redefine a AAA in women and the need for a larger study for screening in asymptomatic women over 70 years of age without risk factors and over 50 years of age with risk factors especially smoking (active and ex-smoker) and positive family history. Smoking is an important risk factor for AAA; men who smoke tobacco are 2.5 times more likely to develop an AAA than men who are non-smokers in their lifetime. After the age of 65 years this risk increased by 40 per cent every 5 years.[26]

FAMILIAL AAA

There has been emerging evidence suggesting a strong link between family history and development of AAA. There have been several studies in the literature now, including population-based studies, suggesting a genetic predisposition to AAA disease.[27,28] Furthermore, the presence of AAA disease in 1st degree relatives increases the risk of developing the disease by twofold.[28-30]

Researchers have studied the prevalence of AAA among relatives of AAA patients using three methods in the literature: 1) collecting family information through interviews and family history questionnaires; 2) USS screening of family members of asymptomatic AAAs; 3) using national registries of hospital discharge and cause of death data.[28]

The Liège AAA family study (n=618 AAA patients), one of the largest studies, utilised the first two approaches for patients in Belgium.[31] The cohort of probands were divided into two groups. First group probands (n=296 patients) were followed up by computed tomography (CT) with PET-CT and family history was collected by the first method described above which is direct questioning. Relatives (≥50 years old) of second group probands (n=322 patients) were contacted and invited for USS screening using the second method described above. It showed about 10% of AAA patients had a family member who had an AAA (proband who has a familial AAA) with a prevalence of 13% amongst affected families (screened relatives); this prevalence is increased even more among siblings, especially brothers, to 25%. Another study of 568 AAA patients in Netherlands using first approach of the interview found that 22.5% of them had a relative with AAA. There was a 2.8-fold higher risk among female relatives, and 1.7-fold higher risk among male relatives than in estimated sex-specific population risk.[30] Clinically, familial AAA cases are unlike sporadic cases as the former constitute slightly younger (average two years younger than their sporadic counterparts) patient group with high-risk of AAA rupture even if it is less than 50 mm size (8% vs 2.4%, p<0.0001).[31] From NAAASP in the UK, AAA rupture rates are very low (<0.5%) in men who are part of the surveillance programme with medium size AAA (4.5-5.4 cm).[32]

A recent study in Sweden, using a Markov 'simulation' model established that targeted screening of first-degree relatives of AAA patients could increase the quality-adjusted life years significantly with gain of 27 per 1000 invited.[33] It used two methods to identify and target siblings of AAA patients. Method A was to identify siblings by direct questioning to AAA patients in a clinical setting, then inviting siblings for screening (n=1860 AAA patients with 2418 living siblings per ten million population per annum), and method B was identification of siblings by registry, then inviting them for screening (n=2748 AAA patients with 3572 living siblings per ten million population per annum). Based on the study analysis, targeted screening of siblings, either by method A or B, of AAA patients can further reduce AAA mortality at an acceptable cost.

Studies which adopted the interview approach, where interviews with AAA patients and mail-in family history questionnaires were used to gather information on family history, found 12% of AAA patients have familial prevalence. In addition, studies who took a second approach of USS scanning all first-degree relatives of AAA patients also established prevalence of 12% among relatives. Larsson et al used the third approach by collecting data from the registry found 8.4% of AAA patients (n=3183) had family history.

Overall in the literature, prevalence of AAA amongst family members has been quoted between 3% and 19% which is higher when compared to general population.[28,31,34-36] This high prevalence of AAA in the first-degree relatives provide a strong argument for aggressive approach to screening of this specific cohort.

The recently published Female Aneurysm Screening Study (FAST) from Leicester (2021) which adopted targeted screening approach for women (aged 65-74 years) with high risk factors (smoking or/and heart disease), concluded that in the population who attended screening, the prevalence of AAA among women with cardiovascular disease was 0.29% for AAA which is much lower than expected 0.35%, above which AAA screening seems to be effective.[37] A retrospective cohort study from France suggested ultrasound screening in women, especially with a positive family history where a first-degree relative is affected, has a prevalence of AAA in this cohort of 8.3%.[38]

There are varying perspectives on recommendations for screening first degree relatives with regards to their age

and sex. According to the society for vascular surgery (SVS2), men >55 years with an affected first degree relative should be screened for AAA (strong recommendation).[39] If a woman has smoked or has an affected first degree relative, she should be screened at age 65 (strong recommendation). However, the European society of vascular surgery (ESVS) recommends: "Screening those with a known family history of AAAs should be evaluated and include both men and women above 50 years of age".[40] Currently it has been recommended that "men and women of 50 years and older with a first degree relative with an AAA may be considered for screening at 10 years interval" (Class IIb, level C).[23] The Canadian society for vascular surgery (2008) propose that "all men aged 65 to 75 years be screened with ultrasonography for an AAA, with additional selective screening for those at high risk for AAA, including women older than 65 years at high risk owing to smoking, cardiovascular disease and family history; and men younger than 65 years with a family history of AAA".[41]

In the literature, there have been no data from a single randomised clinical trial or large nonrandomised studies published with 'targeted USS screening' with regards to family history of AAA. In addition, further studies will be needed to evaluate whether screening adults with a family history of AAA results in better health outcomes.

We propose that it will be prudent to conduct a population-based study in the UK with targeted screening particularly aimed at first-degree relatives of index AAA patients. This screening will be with the 'targeted approach' by actively looking for a selective high-risk cohort, targeting men and women over 50 years of age who are first-degree relatives of the proband-either siblings or children. This study will generate more evidence to determine the usefulness and efficacy of this approach, specifically to investigate the prevalence of familial AAA in probands with a known AAA and the prevalence of AAA amongst family members. It will also investigate the age at which AAA reaches the threshold for surgery in relatives with a familial aneurysm. Based on the studies discussed, we propose to invite first degree relatives at age 50 or older, both men and women, for a screening ultrasound scan using the methodology and standards described within the NAAASP guidelines. If no AAA is found, then a second ultrasound scan at age 60 will be advised. All men at age 65 will be invited for their routine screening ultrasound scan under the auspices of NAAASP.

CONCLUSION

Prevalence rates for AAA amongst males at age 65 detected by screening appear to be decreasing, however AAA screening continues to be cost effective. The prevalence amongst targeted high-risk groups exceeds the population prevalence. Ultrasound screening for first degree relatives, both male and female, of patients with AAA appears to be feasible and cost effective. A pilot study to determine the prevalence of familial AAA amongst probands and the prevalence amongst first degree relatives should identify the unmet need for AAA screening for this cohort and quantify the resources required for a sustainable screening programme.

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