Abdominal Aortic Aneurysm – Different Aspects on Screening

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Abstract

Abdominal aortic aneurysm (AAA) is a hideous life threatening disease that most often is asymptomatic until it ruptures. Ruptured abdominal aortic aneurysm (rAAA) is a painful and serious predicament with a mortality of 80-90%. Half of the patients die before arriving to hospital, leaving family members in sorrow and shock. In Sweden about 700-1000 patients die each year due to rAAA, corresponding to 1.5% of all deaths in men.

Four randomized trials have shown that screening for AAA is cost-effective to reduce both AAA related mortality by 50% and all-cause mortality by 3%. These trials have been the reason why screening 65 year-old-men for AAA has been introduced in Sweden.

In this thesis we evaluated different aspects on screening for AAA.
Study I; the aim was to study whether a biological marker (APC PCI complex) may be used as a screening marker for AAA in patients with peripheral vascular disease without previously known AAA. However, the sensitivity and specificity were both to weak to be used as a screening marker for AAA in the clinical praxis. Nevertheless, we discovered that the prevalence of AAA was 13% in patients with peripheral vascular disease.

Study II; the aim was to investigate the impact of socioeconomic status (SES) and demographical aspects on compliance to AAA-screening and also to evaluate the associations between AAA prevalence and SES. Our results indicated that the prevalence of AAA is higher in demographic areas with lower SES. The compliance to AAA-screening was also lower in areas with lower SES.

Study III; the aim was to investigate if a collaboration between a professional advertising agency and an academic vascular unit can result in increased compliance to AAA screening. The results showed that compliance to AAA-screening can be increased significantly by consulting an advertisng agency.

Study III; the aim was to evaluate if screening is still cost-effectivley in the new era of decreased AAA prevalence, EVAR as the predominant treatment method and improved medical treatment. By using a Markov model we could show that it is still cost-effective to screen for AAA even with the aformentioned changes.

In conclusion; Screening for AAA seems justified in the new era of changing prerequisites. However, importance of SES and different aspects on improving AAA compliance are of great importance and need to be studied further.

Key words
Abdominal aortic aneurysm, screening, biomarkers, socioeconomic status

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To Lina and Leonard

Contents

Abbreviations

3D	Three dimensional
AAA	Abdominal aortic aneurysm
ACE	Angiotensin converting enzyme
AHA	American Heart Association
AMI	Acute myocardial infarction
AMPKα2	AMP-activated protein kinase alfa 2
Ang II	Angiotensin II
APC	Activated protein C
ApoA-I	Apolipoprotein AI
ARB	Angiotensin receptor blocker
AUC	Area under the curve
BB	Beta blocker
CAD	Coronary artery disease
Chi^2	Chi-squared distribution
CI	Confidence interval
CKD	Chronic kidney disease
CRP	C-reactive protein
CT	Computer tomography
CTA	Computer tomography angiography
CUA	Cost-utility analysis
DIC	Disseminated intravascular coagulation
DM	Diabetes mellitus
DSA	Digital subtraction angiography
DVT	Deep venous thrombosis

ECM	Extracellular matrix
EPCR	Endothelial cell protein C receptor
EQ5D	European quality of life-5
ESH	European Society of Hypertension
EVAR	Endovascular aortic repair
FDR	First degree relatives
HRQoL	Health-related quality of life
HDL	High-density lipoprotein
HMG-CoA	Hydroxyl-methyl-glutaryl-CoA
HUI	Health utilities index
ICAM	Intercellular cell adhesion molecule
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IFN	Interferon
IGF	Insulin-like growth factors
IL	Interleukins
ITI	Inner-to-inner
IVUS	Intravascular ultrasound
LDL	Low-density lipoprotein
LELE	Leading-edge to leading-edge
MASS	Multicentre aneurysm screening study
mmHg	Millimeters of mercury
MMPs	Metalloproteinases
MRA	Magnetic resonance angiography
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPV	Negative predictive value
NSF	Nephrogenic systemic fibrosis
OPG	Osteoprotegerin

OPN	Osteopontin
OR	Open repair
OR	Odds ratio
OTO	Outer-to-outer
PAD	Peripheral atherosclerotic disease
PAI-1	Plasminogen activator inhibitor type 1
PCI	Protein C inhibitor
PE	Pulmonary embolism
QALYs	Quality adjusted life years
rAAA	Ruptured abdominal aortic aneurysm
RAS	Renin angiotensin system
RCT	Randomized controlled trial
ROC	Receiver operating characteristic
ROS	Reactive oxygen species
SE	Standard error
SES	Socioeconomic status
SF-6D	Short form 6 dimensions
SG	Standard gamble
SNP	Single nucleotide polymorphism
TG	Triglyceride
TAT	Thrombin-antithrombin III complex
TIMP	Tissue inhibitors of matrix metalloproteinase
TNF	Tumour necrosis factor
tPA	Tissue plasminogen activator
TTO	Time trade-off
US	Ultrasound
USPSTF	United States Preventive Services Task Force
VAS	Visual analogue scale
VCAM	Vascular cell adhesion molecule

VSMC	Vascular smooth muscle cells
WHO	World Health Organization

List of publications

The present thesis is based on the following papers, referred to by their Roman numerals and reprinted with consent from the respective publishers.

I. **APC-PCI complex levels for screening of AAA in patients with peripheral atherosclerosis**
Moncef Zarrouk, Kave Keshavarz, Bengt Lindblad, Anders Gottsäter
J Thromb Thrombolysis 2013;36:495-500

II. **The importance of socioeconomic factors for compliance and outcome at screening for abdominal aortic aneurysm in 65-year-old men**
Moncef Zarrouk, Jan Holst, Martin Malina, Bengt Lindblad, Christine Wann-Hansson, Maria Rosvall, Anders Gottsäter
J Vasc Surg 2013;58:50-55

III. **Academic vascular unit collaboration with advertising agency yield higher compliance in screening for abdominal aortic aneurysm**
Moncef Zarrouk, Anders Gottsäter, Martin Malina, Jan Holst
J Med Screen 2014;21:216-218

IV. **Cost-effectiveness of screening for abdominal aortic aneurysm in combination with medical intervention in patients with small aneurysms**
Moncef Zarrouk*, Adam Lundqvist*, Jan Holst, Thomas Troëng, Anders Gottsäter
* contributed equally, (Submitted)

Introduction

Etymology of the medical terms

The word aorta is derived from the ancient Greek word ἀορτή (aorte), originating from the verb ἀορτήέω (aorteo), the lengthened form of ἀείρω (aeiro) meaning "to lift/to raise".[1] The origin of the term stems from the gross anatomic morphology of the continuation of the aorta from the heart, illustrating that the heart is raised from the aorta.

Most probably, the word aorta has its etymological origins from the medical term "artery". Artery derives from the Greek word ἀρτηρία (arteria) which consists of two words, ἀήρ (aer) meaning "air" and τηρείν (terein), meaning "to keep".[2] In ancient times, the common belief was that the arteries were windpipes carrying air since they were empty in cadavers. This was the reason why Hippocrates initially used the word aorta to describe the airways.[3]

The word aneurysm derives from the Greek word ἀνεύρυσμα (aneurysma), which means "a widening/an opening".[4-5]

History

More than 3500 years ago, atherosclerosis has been proven to exist on studies on Egyptian mummies.[6] The author of Ebers Papyrus, one of the earliest medical writings, written 2000 BC, described arterial aneurysms and recommended the following treatment: "Treat it with a knife and burn it with a fire so that it bleeds not too much".[7]

A Greek surgeon, Antyllus, described a therapy of aneurysm in the 2nd century AD, in which he applied ligatures to the arteries that entered and exited the aneurysm and then cut into the sac, evacuating the contents, and then packed the cavity without resecting the sac. Nevertheless, he stated "those who tie the artery, as I advise, at each extremity, but amputate the intervening dilated part, perform a dangerous operation. The violent tension of the arterial pneuma often displaces the ligatures".[8]

Ambroise Paré (1510-1590) advocated to place a proximal ligature to the aneurysm but did not believe in opening the sac because of the danger of fatal bleeding. Paré described the rupture of the thoracic aneurysm "the aneurysm which happen in the internal parts are incurable".[6-7]

Andreas Vesalius (1514-1564), a friend of Paré, was the first to describe abdominal and thoracic aneurysms.[9]

During medieval times, bloodletting by puncture of the median basilic vein was common and as a complication aneurysms developed in the antecubital fossa. Matheus Purmann ligated the artery proximally and distally to the aneurysm and removed the sac in 1680.[7]

John Hunter (1728-1793) studied the development of collateral circulation which resulted in his treatment for popliteal aneurysm by ligating the superficial femoral artery in the region today known as Hunter's canal.[10]

Astley Cooper (1768-1841) was the first to perform a ligation of the aorta in order to treat a leaking iliac aneurysm.[11]

Rudolf Matas (1860-1957) introduced endoaneurysmorrhaphy by obtaining proximal and distal control obliterating the aneurysmal sac, oversewing collaterals and preserving a lumen of blood flow.[12]

Over the years, several methods have been used in order to treat aneurysms, such as, needling, wiring, proximal banding, ligation, cellophane wrapping, and electrothermic coagulation.[13]

The Swedish team Claerence Crafoord and Gustav Nylin reported the first successful end-to-end anastomosis of the aorta in Sweden 1944.[14]

Very important to add is that Wilhelm Kondrad Roentgen discovered x-rays 1895, and in 1923 Barney Brooks introduced the modern angiography by injecting sodium iodide into the arterial system.[15]

A big step forward was when in the beginning of the 1950s (1951-1953) several surgeons performed replacement of the abdominal aortic aneurysm with homograft replacement (Schafer and Hardin, Dubost, Julian, Brock Debakey and Cooley, and Bahnson). [16-21]

In 1966, Oscar Creech combined the aneurysmorrhaphy method of Matas with graft replacement that left the aneurysmal sac in place.[22]

Important to mention is Henry Bahnson[23] who was the first surgeon able to treat a ruptured abdominal aortic aneurysm successfully in 1953, soon to be followed by Gerbode[24], Cooley and DeBakey[25], and Javid[26].

The principle of introducing Vinyon-N cloth grafts as substitute for an artery was presented 1952 by the physicians Voorhees, Jaretski, and Blakemore.[27]

Michael DeBakey developed the principle further by introducing Dacron grafts.[28]

The use of endovascular aortic repair (EVAR) was presented in 1986 by Nikolay Volodos[29], and further clinically applied by Juan Parodi[30] in 1991.

Aortic anatomy

The aorta is the main artery of the body (figure 1) and ascends from the heart, to the right, behind the pulmonary trunk, as the ascending aorta (pars ascendens aortae). The aortic arch is formed when it travels back towards the left, crossing the hilum of the left lung. At the level of the 4th thoracic vertebra, the aorta descends initially on the left side of the vertebral column, and then in front of it as the descending aorta (pars descendens aortae). In the thoracic region the esophagus crosses in front of the descending aorta (thoracic aorta [pars descendens aortae]). The aorta penetrates the diaphragm through the aortic hiatus, and after passing through the aortic hiatus of the diaphragm, the aorta is called the abdominal aorta (pars abdominalis aortae). In front of the 4th lumbar vertebra, at the level of the umbilicus, the abdominal aorta divides at the aortic bifurcation (bifurcatio aortae) into the right and left common iliac arteries. Both the left and the right common iliac arteries emanate into one branch into the pelvis, the internal iliac artery and one branch to the leg, the external iliac artery. The final unpaired continuation of the aorta is a remnant of a tail artery, the middle sacral artery.[31]

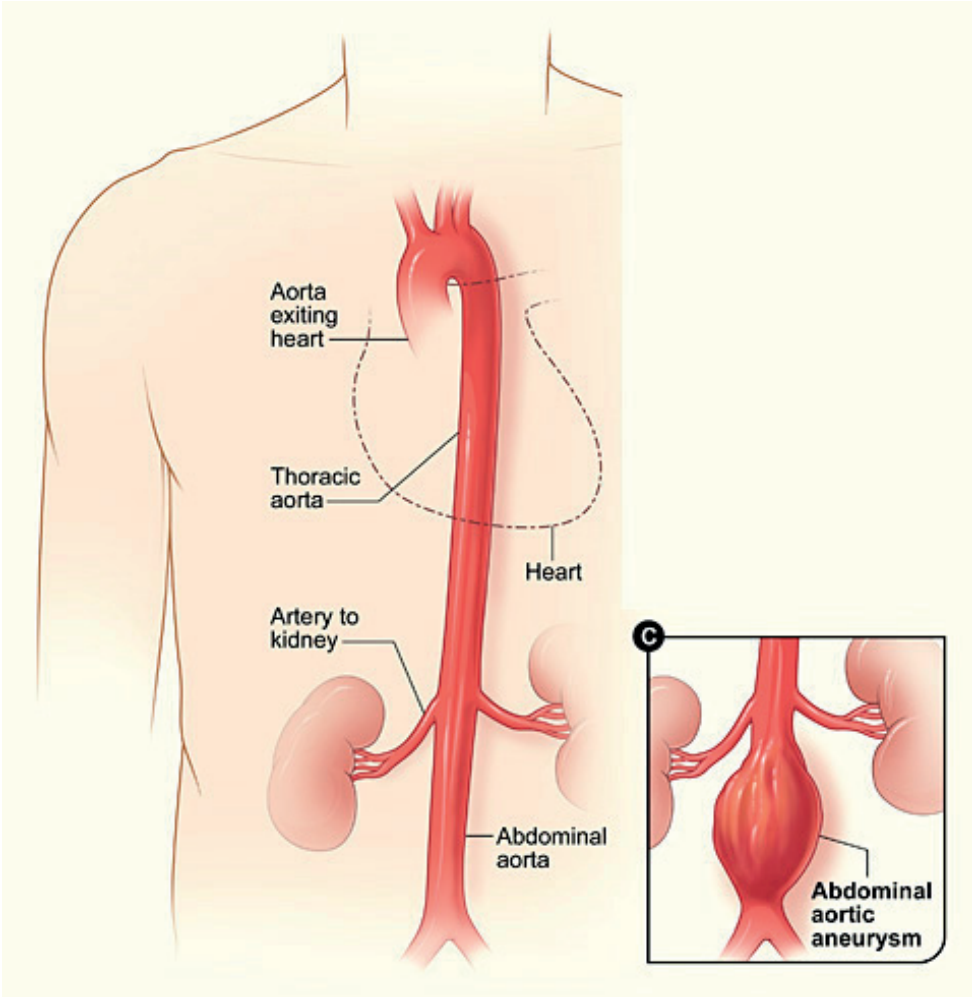

Figure 1.
The aorta and an infra-renal abdominal aortic aneurysm (c).

Abdominal aortic aneurysm (AAA)

Definitions

There are several definitions of AAA and by far the most widely accepted is a permanent, localized (focal) widening of the abdominal aortic diameter of 3.0 cm or more, representing a 50% increase of a normal (2 cm) aortic diameter. This is usually more than two standard deviations above the normal aortic diameter for both genders.[32-34] In order to compensate for individual variation in the diameter of the adjacent aorta, it has also been suggested to define AAA as the maximum infra-renal aortic diameter being at least one and a half times larger than the expected normal infra-renal aortic diameter.[35]

The infra-renal part of the aorta is the most common site for aneurysm formation.[36]An authentic aneurysm involves widening of all the three mural layers of the vessel wall (the intima, the media, and the adventitia) (figure 2) whereas "false" aneurysms develop as a consequence of injuries to the vessel walls and are beyond the scope of this thesis.[37] However, there are two morphological types of aneurysms: the first one is fusiform, the most common one, affecting the whole circumferential of the artery and the second one is saccular, involving only a portion of the circumference with a characteristic outpouching of the layers of the vessel and is more prone to rupture.[38]

Furthermore, an AAA can be classified depending on its anatomy in relation to the renal arteries. An infrarenal aneurysm originates distally to the renal arteries and a juxtarenal aneurysm emanates from the level of the renal arteries without any normal aorta between extent of the aneurysm and the renal arteries. A suprarenal aneurysm involves the splanchnic and renal arteries or the renal arteries only.[39]

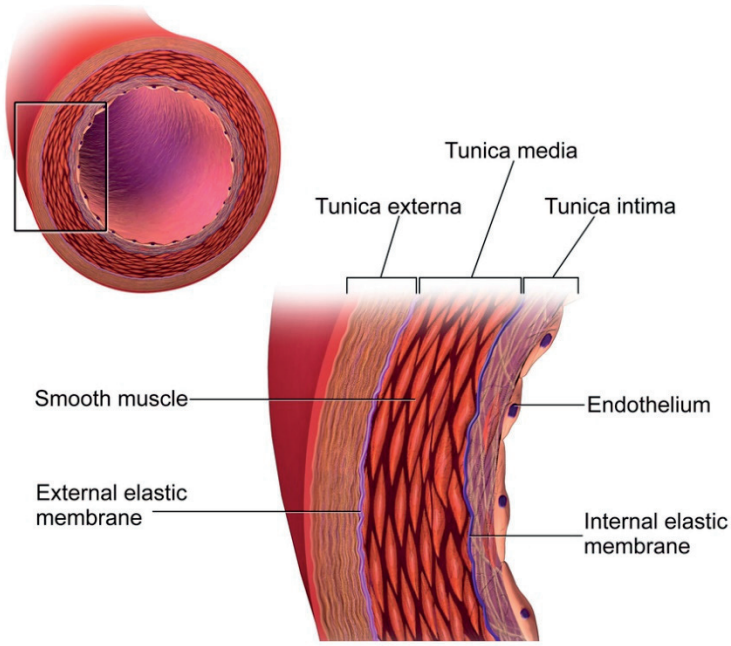

Figure 2.

The anatomy of the aortic wall.

Physiology

The tangential stress (τ) within the wall of a fluid-filled tube shaped like a cylinder can be expressed as

$$\tau = P\frac{r}{\delta} \qquad \text{(a)}$$

Where P is the pressure exerted by the fluid (in dyne/cm^2), r is the internal radius (cm), and δ is the thickness of the tube wall (cm). The tangential stress is directly proportional to pressure and radius but inversely proportional to the wall thickness. The equation (a) is similar to Laplace's law (b), since it defines tangential tension (T) as the product of pressure and radius.

$$T = Pr \qquad \text{(b)}$$

Tension is given in units of force per tube length (dyne/cm). The terms "stress" and "tension" have different dimensions describing the forces acting on the tube wall in different ways. Laplace's law can be used to characterize thin-walled structures such as

soap bubbles albeit it is not suitable for describing stress in arterial walls. Current clinical assessment methods to evaluate AAA rupture risk are unreliable.[37,40]

Pathology, pathogenesis, and pathophysiology of AAA

The aorta is composed of three different layers, the intima, the media and the adventitia (figure 2). The innermost layer of the aorta, the intima, is in direct contact with the blood. This layer is composed of endothelial cells, and the production of reactive oxygen species (ROS) by these cells may contribute to the formation of aneurysm.

The middle layer, the media, is composed of extracellular connective elements such as elastin, collagen type I/III, proteoglycans and vascular smooth muscle cells (VSMCs) forming units.[37,41]

These load-bearing units serve to maintain the integrity of the aortic wall in a healthy vessel, however, these units are significantly reduced over a period of years to decades during aneurysm formation. By time, the degradation of elastin together with the deposition of collagen will increase the aortic stiffness.

Rupture is the final stage of the disease, occurring when residual and newly produced medial and adventitial collagen fibers fail to maintain integrity.

The outermost layer, the adventitia, is composed of fibroblasts, collagen, nerve fibers and vasa vasorum and is also a part of the aneurysm formation.

Histological studies of human AAA specimens show that the three pathological hallmarks of AAAs are leukocytic infiltration, degradation of extracellular matrix (ECM) and depletion of VSMC.[42-44]

Due to the difficulties achieving AAA specimens at an early stage, most of this research has been based on mouse models.

The most used mouse models are; adventitial exposure to calcium chloride, transient perfusion of elastase into the infrarenal aorta, and chronic subcutaneous infusion of angiotensin II.[45] Conclusions based on the above mentioned mouse models have indicated that aneurysm development involves local inflammatory responses leading to the infiltration of macrophages, neutrophils, mast cells and T and B lymphocytes.[46] Cytokines and extracellular proteases will further enhance the inflammatory response and finally result in VSMC apoptosis and ECM degradation.[45,47]

Leukocytes and mast cells

Macrophages are the most prominent cells present in the media and adventitia in AAA, yet their role in the aneurysm formation is not fully understood.

Neutrophils are also present in the aneurysmal wall, and transported from the plasma into the aortic wall by L-selectin adhesion molecules.[48]

Mast cells are able to produce and release inflammatory factors and proteases and their presence in the aortic wall contributes to aneurysm formation by its degradation of the wall.[49]

Chemokines and cytokines

Cytokines have the ability to regulate leukocyte activity and function by their pro-inflammatory and anti-inflammatory properties, and tumour necrosis factor (TNF)-α and (TNF)-β have been shown to be upregulated in plasma of patients with AAA. Furthermore, Interleukins (IL) have a regulating role in inflammation and cellular apoptosis, and during a chronic inflammation there are increased levels of IL, such as IL-1β, IL-6, IL-17 and IL-23 in patients with AAA compared to controls.[50-51]

Proteases

In order to prevent rupture of the aorta, it is important that the structural integrity of the wall is maintained by both elastin and collagen. Several studies show that the degradation of these two proteins in the media results in a weakening and finally a widening of the aortic lumen.[52-53] Several proteases and their inhibitors have been associated with AAA formation, including, matrix MMP, serine proteases and cysteine proteases.[46] The MMPs are zinc endopetidases, and the most studied MMP in the formation of aneurysms is MMP-9, followed by MMP-2, and MMP-12.[52]

Biomarkers in AAA

It would be clinical desirable to use a biomarker for diagnosis, surveillance, and estimation of rupture risk of AAA. At present time, no biomarkers have sufficient high sensitivity and specificity to be used in the clinical praxis, however. The following section about biomarkers is a summary based on a recent meta-analysis.[54]

Fibrinogen: The pooled analysis of data indicates that patients with AAAs have significantly higher plasma concentrations of fibrinogen compared to controls. Previously, a positive association between AAA size and plasma fibrinogen was suggested, however, meta-regression did not confirm such an association.

D-dimer: The pooled analysis of data indicates that patients with AAAs have significantly higher plasma concentration of D-dimer compared to controls. Similarly, meta-regression has shown a highly significant, strongly positive association between the diameter of the aneurysm and the D-dimer concentration.

Tissue plasminogen activator (tPA): Pooled data analysis indicates that plasma concentrations of tPA in patients with AAA do not significantly differ from those in patients without AAA.

Plasminogen activator inhibitor type 1 (PAI-1): No significant differences in plasma PAI-1 concentrations have been shown between patients with AAA and patients without.

Plasmin-antiplasmin complexes: One study has shown that the plasmin-antiplasmin complex is significantly positively correlated with AAA expansion rate.

Thrombin-antithrombin III complex (TAT): Pooled data revealed that patients with AAAs have a significantly increased plasma concentration of TAT, whereas no significant association between AAA diameter and TAT concentration could be shown.

Prothrombin fragments F1+ F2: The pooled data analysis could not reveal any significantly differences in plasma concentration of F1 or F2 between patients with AAA and patients without.

Platelet count: The pooled data analysis showed no significant differences between platelet counts of AAA patients and controls.

Metalloproteinase (MMP)-9: The pooled data analysis showed significantly higher levels of MMP-9 in AAA patients compared to controls.

Tissue inhibitors of matrix metalloproteinase (TIMP) 1: The pooled data analysis showed significantly higher levels of TIMP-1 in AAA patients compared to controls.

α1-Antitrypsin: The pooled data analysis showed significantly higher levels of α1-Antitrypsin in AAA patients compared to controls.

C-reactive protein (CRP): The pooled data analysis showed significantly higher levels of CRP in AAA patients compared to controls.

Interleukins (IL): The pooled data analysis showed significantly higher levels of IL-6 in AAA patients compared to controls.

Lipoprotein(a): The pooled data analysis showed significant higher levels of lipoprotein (a) in AAA patients compared to controls.

Interferon (IFN) γ: Significantly increased IFN γ levels have been shown in women with AAA compared to controls, whereas such associations could not be shown in men.

Intercellular cell adhesion molecule (ICAM) 1 and Vascular cell adhesion molecule (VCAM)1: Both ICAM 1 and VCAM 1 have been shown to be significantly increased in patients with AAA compared with controls.

Caeruloplasmin: Only one study has evaluated caeruloplasmin in AAA patients in comparison to controls, showing significantly increased levels of caeruloplasmin in AAA patients.

Triglyceride (TG): Pooled data analysis showed significantly higher levels of TG in AAA patients compared to controls.

High-density lipoprotein (HDL): Pooled data analysis showed significantly lower levels of HDL in AAA patients compared to controls.

Low-density lipoprotein (LDL): Pooled data analysis showed no significant differences in LDL levels between AAA patients and to controls.

Cholesterol: Pooled data analysis showed no significant differences in cholesterol levels between AAA patients and to controls.

Apolipoprotein A-I (ApoA-I): Pooled data analysis showed significantly lower levels of ApoA-I in AAA patients compared to controls.

Insulin-like growth factors (IGF): Patients with AAA had higher levels of IGF compared to controls.

APC-PCI complex

Activated protein C (APC) is a serine proteinase regulating blood coagulation.[55] In order to activate protein C, thrombomodulin together with thrombin are both needed to form a complex, and this process is enhanced when protein C is bound to the endothelial cell protein C receptor (EPCR).[56] APC reduces the formation of factor Xa and thrombin by cleaving factor VIIIa and Va, the cofactors of the active forms of coagulation factors IX and X (factors IXa and Xa).

APC is inhibited by members of the serine proteinase inhibitor family[57-60], whereof the most important inhibitors of APC are protein C inhibitor (PCI) and α_1-proteinase.[61-63]

Plasma concentration of APC-PCI complex has been shown to be increased in hypercoagulative states such as deep venous thrombosis, pulmonary embolism, acute myocardial infarction, disseminated intravascular coagulation, and chronic renal failure.[64-67]

Strandberg et al[68] have developed a immunofluorometric sandwich assay by employing a mouse monoclonal catcher antibody (M36) that recognizes a conformation-dependant neoepitope in PCI. This neopepitope is expressed only on PCI that is in complex with APC or that has been cleaved and dissociated from the complex.[68] The antibody has a high affinity for loop-inserted PCI whereas the affinity for native PCI is too low to be measured. As a tracer the labelled mouse monoclonal antibody against protein C is used. This method for measurement of APC-PCI complex allows accurate measurements of concentrations in plasma with a linear dose-response curve.[68]

Epidemiology

Risk factors

Risk factors can be classified as modifiable and non-modifiable. Non-modifiable risk factors are race, ethnicity, genetics, gender, and family history.

Several risk factors are known for the development of AAA such as advanced age, cigarette smoking, family history, hypertension, obesity, hypercholesterolemia, and atherosclerotic occlusive disease.[37] Obesity, defined as a waist-to-hip ratio greater than 0.9, is an independent risk factor for AAA in men, and serum levels of the proinflammatory adipokine resistin correlate strongly with aortic diameter.[69]

Female gender, African-American race, and diabetes mellitus are associated with reduced risk of developing AAA.[70] On the other hand, patients with inherited connective tissue disorders, such as Marfan's syndrome, Ehlers-Danlos syndrome, gonadal dysgenesis, neurofibromatosis type 1 (von Recklinghausen disease), Menkes' kinky hair syndrome and tuberous sclerosis are predisposed to aneurysm formation.[37]

Smoking

Smoking is the strongest risk factor for AAA (with odds ratio [OR] > 3.0).[70-71] An association between nicotine and AAA formation has been seen in animal models, where nicotine stimulates AMP-activated protein kinase alfa 2 (AMPKα2) in vascular smooth muscle cells, resulting in a release of MMPs.[72] Smoking contributes to at least a 3.5- fold increase in relative risk (RR) compared to the other AAA risk factors. Consequently, it is understood that the relationship between smoking and AAA development is stronger than relationships between smoking and other diseases such as stroke and acute coronary syndrome[73-77], the only exception being the relationship between smoking and lung cancer. [74,78-80]

Furthermore, smoking is also associated with an almost double aneurysm expansion rate compared to previous or non-smokers.[71]

So, smoking accounts for almost 75 % of all aneurysms above 4 cm[76], and people who smoke 20 cigarettes daily have a 12- fold- increased risk for developing an AAA compared to non-smokers.[81]

Snuff is a smokeless tobacco that is commonly used in Sweden. Approximately 12.7% of all Swedish men between 65 and 69 years of age use snuff on a daily basis. For daily smoking this figure is 13.5%.[82] Potential effects of snuff on AAA are not well studied, but as the effects of snuff on cardiovascular morbidity are harmful snuff use should be avoided.[83-84]

Age

Age is a non-modifiable risk factor for AAA. With increasing age, the prevalence of AAA increases so that OR for AAA in subjects older than 54 years are 2.76 at 55-59 years, 5.35 at 60-64 years, 9.41 at 65-69 years, 14.46 at 70-74 years, 20.43 at 75-79 years, and 28.37 at 80-84 years.[85] According to a Swedish autopsy study, the prevalence of AAA increases continuously after the age of 55 among men and reaches a peak of more than 10% in those between 80 to 85 years old. The highest prevalence of AAA in women are around 5% at the age of 85 years or older.[86]

Heredity

It is well known that patients with a family history of AAA also have an increased risk of AAA development[79,87-88] and it has been shown that between 12-19% of first-degree relatives (FDR) to patients operated for AAA have AAA themselves.[89-91] A Swedish study demonstrated that the RR for developing AAA among FDR of patients with AAA was almost doubled compared to those without FDR with AAA.[91] The first strong hereditary association of AAA was demonstrated in 1977, in three brothers all treated for AAA.[92] The overall prevalence of AAA in siblings evaluated in a Swedish study was 11% (17% in men and 6% in women).[93] Several genes have been associated with AAA, such as the single nucleotide polymorphism (SNP) MMP3 rs3025058, chromosomes 16, 4q32-34, 11q24 and 9p21.[94-96]

Lifestyle

The most dangerous behavioral risk factor for premature mortality is tobacco use[98], and those with lower socioeconomic status SES are more likely to use tobacco.[99] By increasing tobacco taxes, the tobacco prices will increase, and this could result in a reduced tobacco consumption.[100] Smoking rates are declining in Sweden[101] as taxes on tobacco are increased, and it will be interesting to evaluate these effects further in the future on health and vascular diseases. A sedentary lifestyle together with lower consumption of fibers, fresh fruits and vegetables have been established for those with a lower SES.[100]

Prevalence

$$\text{Prevalence} = \frac{\text{Numbers of existing cases}}{\text{Population at risk}}$$

Population based screening for AAA is the best way to evaluate AAA prevalence.[70] In the four randomized trials of AAA screening, the prevalence varied between 4.0% and 7.6% in men and was 1.3% in women.[102-105] As previously described, AAA prevalence is associated with age, gender, and geographical location. The prevalence is lower in blacks, Asians, and patients with diabetes mellitus.[70]

In a Swedish necropsy study[85] from 1992, the prevalence of AAA was 4.3% in men and 2.1% in women, and the latest prevalence figures from Sweden in 2011 and 2013 have decreased to 1.5-1.8% in men and 0.4% in women.[106-109] However, since autopsy rates have also declined since 1992, todays best estimates concerning prevalence emanates from screening.[70]

The reason for the decreasing prevalence is most likely the decreasing smoking rates in 65-year-old men.[101]

AAA expansion rate

AAA expansion rates differ with time and aortic diameter, however, the average AAA grows at a rate of 2 to 3 mm per year. Importantly, aneurysm expansion rate correlates with baseline diameter, in other words, larger AAA grow faster compared to smaller ones in an exponential manner rather than linearly. In patients classified as current smokers, the expansion rate is increased by 20%, whereas in patients with diabetes mellitus the expansion rate is reduced by 30%[69,78,110-112]. Comparing men and women with AAA and similar risk profiles, women tend to have faster expansion rates.[113]

Diagnosis

Abdominal palpation is an old safe clinical method to diagnose AAA. Depending on the AAA size and the abdominal circumference of the patient, the sensitivity of abdominal palpation is 68% and the specificity 75%.[114-115]. Those figures are too low for palpation to be used as the only diagnostic tool nowadays.

Duplex ultrasound (US) is the preferred imaging method for detection and surveillance of AAA in asymptomatic patients.[116-118] Ultrasound has many attractive properties, such as its low cost, noninvasivity, and its sensitivity of 98% and specificity of 99%.[78,119-120] US is, however, operator and equipment dependent.[121] In rare circumstances it is not possible to visualize the abdominal aorta due to technical reasons such as bowel gas or aortic depth.[122] There are different methods for measurement of abdominal aortic diameter (outer-to-outer [OTO], inner-to-inner[ITI], or leading-edge to leading-edge[LELE]). In Sweden the LELE technique is used in ultrasound screening for AAA.[123]

Digital subtraction angiography (DSA) is an imaging method less frequently used nowadays. It can visualize the true lumen of the aortoiliac arteries and its side branches. Still, since it visualizes the true lumen of the aorta, there is a risk to underestimate the aortic size due to intramural thrombosis. The use of iodinated contrast media, as well as the invasive nature of the method are the major drawbacks.[70]

Intravascular ultrasound (IVUS) is an invasive method that requires significant skill both when executing the examination as well as interpreting the data. The method itself does not use any contrast media and has the ability to accurately measure aortic diameter. [70,124-125]

Computed tomography angiography (CTA) is the method of choice in case of preoperative planning for both EVAR and open repair (OR)[70,126], since it can provide detailed information of all vessels and their surrounding anatomy[127-128]. The introduction of three dimensional (3D) images with CTA has further popularized this method in the preoperative setting, especially since EVAR is increasingly used as an operative method.[129] The major drawback of CTA is the use of radiation and nephrotoxic contrast media.

Computed tomography (CT) is sometimes needed in screening cases in which ultrasound is inconclusive, and enables information about an AAA and the surrounding anatomy. However, it is not optimal in the preoperative planning for EVAR since the arterial anatomy including its side branches is not visualized adequately. Nevertheless, CT is the preferred method for diagnosis of ruptured abdominal aortic aneurysm (rAAA).[130]

Magnetic resonance angiography (MRA) can be used for pre-operative planning[131] Contrast media is not necessary but enhances image quality. Nephrogenic systemic fibrosis (NSF) caused by gadolinium is a serious but rare side effect, however. Since MRA does not use radiation and is comparable to CTA for measurement of aortic diameter[70,132] , it will probably be used more frequently in the future. Presently MRA is more expensive, more time consuming, and not suitable for patients with metal implants or suffering from claustrophobia.

Treatment

Surgical therapy

Dubost et al[17], introduced the modern operative technique for open AAA repair in the early 1950s. Since then it has been regarded the standard treatment for AAA. OR is classified as a high risk surgical procedure, due to its long duration, aortic clamping, and stress from blood loss and fluid shifts. Since 2/3 of patients with AAA have angiographic evidence of coronary disease, and only 1/3 are asymptomatic[133-135], ischemic heart disease is the major cause of per- and postoperative mortality. Furthermore, postoperative treatment at an ICU is stressful, and patients have longer convalescence time and subsequently higher risk of complications such as venous thromboembolisms and infections. Nevertheless, since the method has been used for almost 70 years, we have good knowledge of its patency and durability, and therefore this method is often preferred in younger patients. Another great advantage is that normally no follow-up is needed with ionizing radiation such as CT. The average 30-day mortality rate after open repair is 5.5%.[136]

EVAR (figure 3) was introduced in the beginning of the 1990s by Volodos[137] and Parodi[30]. EVAR is classified as intermediate risk surgery[138], is significantly less invasive, and has a shorter post-operative convalescence time compared to open repair. Meta-analysis showed an operative mortality rate of 3.3% (95% CI 2.9-3.6). However, due to increased operative experience, better techniques and perioperative treatments, recent results show mortality rates at 1.4%.[139]

On the contrary, a major drawback is the lack of long-term efficacy of EVAR as compared to open repair. Also, lifelong imaging surveillance is required to detect potential complications such as endoleaks, migration and ruptures. Head-to-head comparisons between EVAR and OR were done in the late 1990s in the UK (EVAR-1)[140-142], the Netherlands (DREAM)[143-145], USA (OVER)[146-147], and France[148]. In a recent meta-analysis[149] the conclusion was that EVAR was associated with a 66% relative reduction in operative mortality (30 day, all-cause mortality). This difference was, however, no longer present at long-term follow up (>2 years). A higher re-intervention rate was also observed in the EVAR group.

A Cochrane review showed no evidence justifying surgical treatment of small aneurysms (4.0 cm to 5.5 cm).[150]

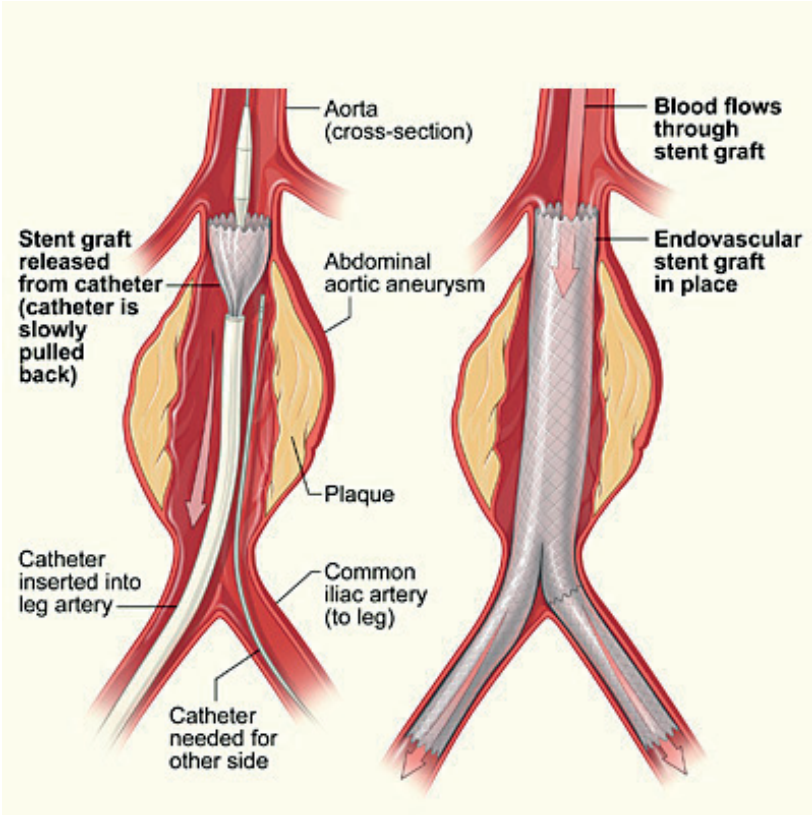

Figure 3.
The principle of EVAR.

Medical therapy

The ultimate goal with medical treatment for AAA would be to stop growth, prevent rupture, allow shrinkage of the aneurysm to a normal diameter, and prevent death from other cardiovascular diseases. No such treatment exists to date, however.

Recommendations on preoperative medical optimization concerning patients with AAA can be found in European Society of Cardiology (ESC) guidelines.[138]

Beta blocker (BB)s: The mechanism by which BB have been proposed to reduce growth of AAA is by reducing shear stress on the vessel wall. This is achieved by reducing heart rate, resulting in a longer diastolic filling period and a decreased

contractility and ultimately decreased myocardial oxygen demand.[138] This is also the theoretical reason why BB exert secondary preventive effects on cardiovascular disease. Two meta-analyses[151-152] have not been able to show significant effects of BB upon AAA growth rate, however.

Even though BB are no longer considered as first line treatment of hypertension in general according to ESH[153], they are still considered as first-line treatment for hypertension in patients with AAA.[153]

Statins: Statins have a lipid lowering effect, which is desirable in patients with hyperlipidemia to slow down the atherosclerotic vascular process leading to cardiovascular events. Furthermore, they have pleiotropic effects which are independent of lipid lowering.[154] The main effect of statins is the inhibition of cholesterol and isoprenoid synthesis leading to an upregulation of the endothelial nitric oxide synthase necessary for vascular wall function. Antioxidant effects occur through inhibition of isoprenoid synthesis[155] by inhibition of hydroxyl-methyl-glutaryl-CoA (HMGCoA) reductase. Inflammatory markers such as C-reactive protein (CRP) have been shown to be reduced after statin treatment, and anti-inflammatory effects have also been suggested. Other potential pleiotropic effects of statins are immunomodulation, normalization of sympathetic outflow, plaque stabilization, decreased activation of blood coagulation, and inhibition of platelet aggregation.[155]

In addition, statins decrease the expression of MMPs, which have an important role in the pathogenesis of AAA.[156-157]

Several meta-analyses have failed in demonstrating significant evidence for reduced AAA growth or rupture rates with statin treatment. However, the meta-analyses did show survival benefits for those on treatment.[158-159] Hence, statins are recommended for all patients with AAA to reduce cardiovascular risk even though no randomized trials have been conducted on statins concerning AAA rupture and growth. It has to be kept in mind, however, that the final answer to this question may very well be modified in the future.

Antibiotics: Tetracycline inhibits MMPs in the vessel wall of AAA.[160-161] The use of doxycycline did not significantly prevent AAA growth or rupture[162], however, a trial using higher dosage of doxycycline is ongoing.[44] In a Swedish RCT, azithromycin did not have any effect on AAA expansion.[163]

Angiotensin converting enzyme inhibitors (ACE) and Angiotensin type 1 receptor blockade (ARB): Infusion of angiotensin type II into animal models results in aortic inflammation and proteolysis which are the causes of AAA formation, rather than the untreated high blood pressure itself.[44,164-166] At the moment there are conflicting results concerning AAA and treatment with ACE inhibitors and ARB; one case-control study suggested reduced rupture rates[167], whereas the United Kingdom Small AAA study[168] showed increased growth rates and the Chichester study[169] showed

beneficial effects on AAA. Large randomized controlled trials (RCT) are therefore warranted in order to establish a consensus.

Antiplatelet therapy (aspirin): Antiplatelet therapy has been suggested to decrease formation of intramural thrombus, stabilize the arterial wall, and reduce inflammation at the site of the AAA.[170] No RCT has been conducted to evaluate reduction of growth and rupture of AAA, however, conflicting data exist. Two studies[167,171] did not find any reduction of AAA growth with aspirin, whereas a Swedish study[163] did show that aspirin was associated with reduced AAA growth.

Aspirin has been proposed to patients with AAA as secondary prevention, due to their high prevalence of concomitant cardiovascular disease.[70,172]

Future medical therapy: At the moment four different clinical trials[44] are investigating medical management of AAA, all with aneurysm growth rate as primary outcome. These studies evaluate an anti-inflammatory drug ([NCT02007252], subcutaneous ACZ885), drugs affecting the renin angiotensin system ([NCT01683084, NCT01118520, NCT01904981], Telmisartan, Perindopril, Valsartan), an antiplatelet drug ([NCT02070653], Ticagrelor), and protease inhibition ([NCT01756833], Doxycycline).[44]

Hypertension: Patients with AAA and hypertension should be treated in order to reduce cardiovascular morbidity. The goal blood pressure is 140/90 mmHg and 140/85 mmHg for patients with diabetes mellitus.[70,153]

Smoking: Because of the strong association between smoking and AAA formation, expansion, and rupture as well its overall unhealthy effect on our biological system, smoking and other kinds of tobacco use should be avoided. Smoking cessation reduces the risk of AAA development[71,77], and also appears to reduce aneurysm growth rate by 20-30%.[113]

Lifestyle: For overall cardiovascular health the American Heart Association (AHA) recommends at least 30 minutes of moderate-intensity aerobic activity at least 5 days per week, or 25 minutes of vigorous aerobic activity at least 3 days per week.[173]

Furthermore, AHA recommends a dietary pattern emphasizing an intake of vegetables, fruits, and whole grains, low-fat dairy products, poultry, fish, legumes, vegetable oils, and nuts, and suggests a limited intake of sweets, sugar-sweetened beverages, and red meats.[173]

The above mentioned dietary recommendations should be adapted to appropriate calorie requirement and other medical conditions.[173]

Health economics

Due to the scarce resources available, such as time, technology, capital and labour inputs, the aim of health economics is to maximize benefits given the resources available. In order to do this, an economic evaluation is needed to help decision makers.[174]

Economic modelling is a simulation and simplification of the real world since only the most important components are taken into consideration. It is increasingly used in high income countries when making both local and national health care decisions.

A well designed model should mirror current clinical practice, and be based on the best evidence available. It is also important that models are run for a sufficient period of time, otherwise long-term results could be missed, as well as capturing all relevant costs and benefits that might not be evident from the beginning.[175-176]

Sometimes it may be difficult to get reliable data, and sometimes assumptions are needed due to lack of evidence. Therefore it is highly important that models are transparent and reproducible in order to be validated correctly.

The two most common models are decision trees and Markov models.[175]

A decision tree is a flow diagram illustrating the logical structure of the problem. Decision trees are optimal facing decisions about acute care, diseases that occur once only, and decisions with short time frames. Because of this, decision trees have some limitations. Firstly, a patient in the model can only progress though the model in a unidirectional manner; there is no possibility to jump between different health states. Secondly, there is no time element; all events happen at a single point in time.[174,175]

Markov modelling

The Russian mathematician Andrey Andreyevisch Markov (figure 4) developed the

Markov model, which do not have the previous mentioned limitations. This makes it suitable for evaluation of complex processes happening over time such as chronic diseases, and Beck and Pauker described the use of Markov models for determining prognosis in medical settings in 1983.[176]

Figure 4.

Andrey Andreyevisch Markov.

Markov models are particularly suitable when a decision problem involves a risk that is ongoing over time, such as risk of hemorrhage while on anticoagulant therapy or risk of rupture of an AAA.[174,176]

For economic analysis both costs and utilities are discounted since events occurring later in the model have less impact compared to events occurring earlier.[177-178]

The key feature of Markov models is that each model is composed of finite numbers of health states (Markov states, figure 5), where each patient in the model has to be assigned to only one of the Markov states at any given time. Nevertheless, at the end of each cycle there is a probability that each patient can transfer to another Markov state, governed by different transition probabilities. The probabilities of moving from one Markov state to any of the other Markov states should always add up to 1.

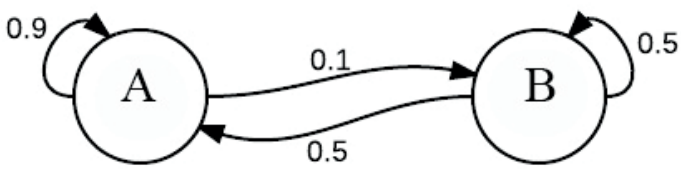

Figure 5.

Scheme of different Markov states (circles) All transition probabilities add up to 1.0 (100%).

When setting up a Markov model, there are 7 important steps:[175]

1. To identify Markov states and possible transitions:

Depending on which clinical situation that is evaluated, different Markov states will be used. Each Markov state has to be mutually exclusive. In other words, a patient can only be in one single Markov state at any given time.

In general, a Markov state is shown as a circle or an oval, and the possible transitions between the Markov states are shown by an arrow (figure 5). An arrow from each circle going back into themselves illustrates how patients will stay in that particular state from one cycle to the next. Some Markov states such as death, have no exits.

2. To determine the length of each Markov cycle

A Markov cycle is the minimum amount of time a patient has to be in a Markov state before a transition to another is possible. The information about the patients during each cycle is constant. Yet, at the end of each cycle, the model re-evaluates what proportions of the population that will change Markov state. This is governed by different transition probabilities.

3. Transition probabilities

At the start of the model, the distribution of the population is defined. The end of each Markov cycle is associated with a possibility to move from one state to another. This is governed by the transition probabilities, and all transition probabilities from each state must equal 1. When finding a transition probability in literature, it is often needed to convert it according to the current Markov model.

4. Outcomes

Outcomes such as life spans or costs are accumulated as long as the model is running.

5. Set the "stopping" rule

When a Markov model is running, the population within the model will eventually die out. Since the models are probabilistic, the population declines exponentially but never reaches zero, and because of this a stopping rule is applied. This is most often done by programming the model to a limited time period when most of the population is expected to be dead, or when the disease has no further clinical relevance.

6. Process of analysis

A "cohort simulation" is the standard way to analyze a Markov model, meaning that a cohort of patients enter at the start of the model and then go through different Markov health states until the model is stopped. During model running, no further

cohorts will enter the model. In that sense the initial number is not relevant, since the percentages of patients in each state are calculated.

7. Validity of the model

First of all, it is important that the structure of the model is consistent with the studied disease and with the issue in question. If assumptions are made, it is important to specify and justify these in the model. Secondly, data should be based on the best evidence available. However, sometimes expert opinion or assumptions can be used due to lack of evidence. Thirdly, consistency of the model must be evaluated. This could be done by internal consistency; by changing variables to their extremes and evaluating the outcome of the model, or by external consistency; by comparing the model´s result at different time points with results from the literature at the same time points.

Generic health status measures

These measures should be broadly applicable across types and severities of disease, different medical treatments or health interventions, and demographic and cultural subgroups. They should also be designed to summarize a spectrum of core concepts of health and quality of life applying to many different diseases, impairments, conditions, patients, and populations.[179]

EQ5D is the only international health index. Five dimensions are included (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The questionnaire consists of only 5 questions, and takes only a couple of minutes to complete, and is therefore a useful tool to add in clinical studies. Its validity, reliability and sensitivity is considerable and shows acceptable standards.[175]

Quality Adjusted Life Years (QALY)

Herbert Klarman introduced the concept of QALY 1968 in a study of chronic renal failure.180 A great advantage of QALY is that it can capture gains from both reduced morbidity (quality gains) and reduced mortality (quantity gains) into one measure. When QALY are used as an outcome, the assessment is knows as a cost-utility analysis (CUA).

In order to generate QALY, health-related quality of life (HRQoL) utilities are needed. These are measured on an ordinal scale of 0-1, where 0 indicates death and 1 indicates perfect health. In order to generate HRQoL weights, there are either direct or indirect methods. The direct methods are visual analogue scale (VAS), the time trade-off (TTO), and the standard gamble (SG). The indirect methods are European

quality of life-5 dimensions (EQ-5D), short form 6 dimensions (SF-6D) or health utility index (HUI).

The advantage of using 1 for perfect health is that the resulting QALY is then measured in units of "perfect health years", meaning 1 year in perfect health equals 1 QALY, and 2 years in 0.5 in health utility equals 1 QALY.[174-175]

AAA screening

Four RCT[102-105] addressing AAA screening were conducted between 1988-1999, all showing reduced aneurysm related mortality for men. The 5-year results showed an OR in favour of screening, with 95% CI of 0.47-0.78.[181] Furthermore, after 13 years of follow-up the Multicentre Aneurysm Screening Study (MASS) trial reported a 3% reduction in all-cause mortality.[134]

A systematic review and two meta-analyses[182-184] concluded that screening for AAA significantly reduces the risk for AAA-related mortality by 45-50% in men aged 65-74 years. Also, there were twice as many elective operations for AAA and half as many emergency operations in the group invited to screening compared to the control group.[134] Screening for AAA with ultrasound fulfills all the below criteria concerning good screening praxis according to the World Health Organization (WHO).[185]

Wilson and Jungner classic screening criteria

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Screening and women

Men have four to six time higher prevalence of AAA compared to women.[106] Out of the four randomized trials[102-105], the Chichester trial was the only one to include women. No significant effects on AAA-related mortality (OR 1.0, 95% CI 0.14-7.07) or all cause-mortality (OR 1.05, 95% CI 0.92-1.19) could be shown after 5 or 10 years of follow up. Importantly however, only 3052 women were included in the study and therefore the negative result may be due to a type two error. The prevalence of AAA is between 0.03-0.60%[75,106] in women who have never smoked, 0.8% in women who have smoked, and about 2% in current female smokers.[75] Therefore, U.S. Preventive Services Task Force (USPSTF), concluded that there is no benefit in screening women who have never smoked. [186] Importantly, as smoking has been increasing in women lately the incidence of AAA may well change in the future.[70]

Sub-aneurysmal aortas

Infrarenal aortic diameters between 25 and 29 mm are by definition considered as normal aortas. However, since it has been noted that these diameters can develop into aneurysmal diameters, they are often sub classified as sub-aneurysmal or as aneurysms-in-formation.[187] In the largest screening RCT, an increased rupture rate in the screened arm which had a normal scan in the beginning of the study was shown after 8 years of follow up. Among scans defined as normal, half were sub-aneurysmal (25-29 mm).[134] At the moment there is no consensus considering the follow-up of sub-aneurysmal aortas, and we have to await study results in order to know if it is cost-effective or not to follow-up aneurysms in formation. In fact, as average expected lifetime is increasing, more ruptures will occur later in life. As smoking rates are decreasing and the use of secondary preventive medication is increasing, this might perhaps not be a significant problem in the future, however.

All of the RCT evaluated screening in men 65 years or older. The reason for this is that the prevalence of AAA increases with age; at age 65 years the prevalence of AAA is high enough for benefit from screening to be shown.[70] Rupture of abdominal aortic aneurysm can occur before 65 years of age, this figure varies between 5-18% in different studies.[79, 188] When a screening result is negative at age 65, however, the risk for future AAA rupture is greatly reduced.[79, 189-193]

Socioeconomic status (SES)

It is a well-known fact that life style factors such as smoking, obesity, overconsumption of alcohol, and physical inactivity are great contributors to premature and preventable mortality and morbidity.[194-200] Socioeconomic indicators as income and education have been shown to be inversely associated with cardiovascular mortality and all-cause mortality.[201-206] It is also acknowledged that people of lower SES to a higher degree are smokers, obese, and have an unhealthy lifestyle.[207-210] There is no doubt that socioeconomic status is clearly linked to morbidity and mortality, however, the mechanisms responsible for this association are not fully understood.[211-212] SES is commonly defined as education, income, and occupation, and underlies three major determinants of health; health care, environmental exposure, and health behavior.[212] According to Weber, socioeconomic status is based on class, status, and party (or power).[213] Class is characterized by ownership and control of resources, and measured by income.[214] Status is characterized by prestige in the community, and based on factors such as family background, lifestyle, and social networks.[214] Finally, power is described in a political context.[213]

Education

The level of knowledge and education can affect behavior and practices by influencing lifestyle, and social networks.[213]

Education is the fundamental SES component since a person with higher education has better chances to get a better job, and thereby also a better income. Also, information and resources to promote health are more easily accessible to people with a higher level of education.[215] Therefore, education is considered to be related to health outcomes due to its influence on lifestyle behavior and problem solving capacity.[216-219]

Income

Income may influence opportunities for education, access to different lifestyles, prestige, and power.[220] A high income will allow a person to purchase better health care as well as consuming healthy and more nutritious food, better housing, schooling, and of course access to recreation.[215] Also, a higher income will make it possible to move to more expensive housing areas with lower environmental pollution. The connection between health and income is stronger at the lowest income levels but the effects of income on health persist also above the poverty level.[221]

Occupation

Occupations could be further sub-classified according to Weber's classes. The first is according to a prestige perspective, mainly based on the public opinions.[222] The second according to a class perspective, based on educational requirements and monetary payoffs.[223] Employed people have better health status compared to those unemployed.[224] By being employed, a person is above a certain threshold both intellectually and physically, otherwise employment would not be possible. Importantly, anticipation concerning job threats, such as being unemployed can effect health, resulting in an increased blood pressure.[215] Employed people have different kinds of occupations, hence different occupational status, qualifications, and rewards. Each of these indicators of occupational status is associated with mortality risk.[224] Occupations with lower status more frequently exposes workers to more physical demands and psychosocial risks[215], such as occupational injury or exposure to toxic substances. A British study has shown differences in coronary heart disease incidences related to workers' occupational grade of job influence.[225] It has been argued that occupation is a reliable single indicator of SES in industrial societies.[226] The three major determinants of health; health care, environmental exposure, and health behavior explain up to 80 % of premature mortality. Health behavior explains 50%, environmental exposure 20%, and finally health care explains 10%.[227]

Socially isolated people have an increased relative risk of mortality ranging from 1.9-5 times, compared to those with better social integrations.[227] Social trust to institutions and society is of great importance, since those communities with greater trust and social structure have lower homicide rates as well as lower overall mortality.[228]

In countries with private health care insurance, there is an association between SES and access to and use of health care, as well as to quality of health care. Many uninsured inhabitants will eventually receive less medical care including screening and treatment.[229] Interestingly enough, also in countries with universal insurance coverage people with lower SES still do not use health care in the same manner as those with a higher SES. It seems that universal coverage is not the solution to a decrease in health inequalities, as the underlying incidence of diseases, environmental exposures and injuries are the dominant forces.[230]

Ethical considerations

All kind of screening programs have benefits and risks, some obvious and other less obvious; this applies also to AAA screening.

The most obvious benefit of AAA screening is decreased AAA-related mortality in patients with AAA needing immediate or future aneurysm repair.[102-105] Furthermore, the rate of elective AAA repair (with less complications) will increase, whereas the rate of emergency repair (with more complications) will decrease.[134]

By inviting apparently healthy 65-year-old men to AAA screening, however, they are exposed to the risk of death during an AAA repair. This is further increased in cases of an overestimation of aortic diameter (overdiagnosis). This risk is low; only one in 10 000 of all men invited for screening will have an AAA which is operated to prevent rupture, and die due to surgical complications.[231]

The number needed to screen in order to prevent one AAA-related mortality is 238.[184]

There is an ongoing discussion about the psychological distress both in patients diagnosed with AAA under surveillance and the patient's family members.[232] More research and long-term follow up are necessary in order to be able to appropriately address this important topic. Yet, some evidence suggests that there is a slight decrease in quality of life after AAA diagnosis, which is no longer detectable after a couple of months.[70] It is also important to stress that the majority of patients screened for AAA will be reassured that they have a normal aorta[70], and potential psychological consequences of such a message also have to be taken into account.

Gender specific screening programs are not uncommon; for example screening for breast cancer in women only as the prevalence of breast cancer is lower in men compared to women. The same concept has been applied to AAA screening as AAA prevalence is much lower in women compared to men. [103,106]

More important is the fact that screening participants must be informed about screening purpose, disease, and treatment. The health care system must be honest and transparent concerning risks with surgical intervention, and properly stress the fact that both screening and treatment if it turns out positive are optional.[231]

Malmö screening data

Data presented in paper II are based on Malmö screening results up to 2012, data in paper III on screening results up to 2013, and data in paper IV on screening results up to 2014. However, as the screening program is currently ongoing, more patients have now been examined. The following data reflect the screening program in our department from the initiation in September 2010 until July 2015.

Men invited: 22 649

Men screened: 17 763

Compliance: 78.4%

AAA detected (≥30 mm): 297 (1.7%)

AAA detected (≥55 mm): 21 (0.12%)

Aneurysm-in-formation (25-29 mm): 536 (3.0%)

Aims

The general aim of this thesis was to evaluate general aspects of AAA screening from an integrated medical and surgical point of view. The different publications are referred to below by their Roman numerals.

-To evaluate if APC-PCI complex can be used as a screening marker for AAA among patients with established PAD but without previously known AAA (I).

-To investigate the potential impact of socioeconomic status (SES) and demographical aspects on compliance to AAA-screening (primary aim, II).

-To evaluate potential associations between AAA prevalence and socioeconomic factors (secondary aim,II).

-To investigate if a collaboration between a professional advertising agency and an academic vascular unit can result in increased compliance to AAA screening (III).

-To evaluate if AAA screening is still cost-effective in the new era of decreased AAA prevalence, EVAR as the predominant treatment method, and improved medical treatment (IV).

Subjects and methods

In this chapter a brief summary of subjects and methods will be described for studies I, II, and IV. For study III a more detailed description will be given since this paper was published as a short communication.

Study I

Between September 2004 and August 2007, 511 patients (age 70[12] years, figure 6) hospitalized at the Vascular Centre at Skåne University Hospital, Malmö for peripheral arterial disease (PAD) were compared to 219 healthy controls; age and sex-matched individuals without symptomatic atherosclerosis and AAA.

APC-PCI complex samples were collected on all patients and investigators were blinded concerning AAA findings prior to APC-PCI complex analysis. Descriptive data were collected as well as 511 measurements of the maximal infra-renal aortic diameter. The Swedish population registry was used for follow-up.

Some of the imaging modalities used for measurements of the abdominal aorta were without contrast media, therefore the prevalence of AAA might have been underestimated.

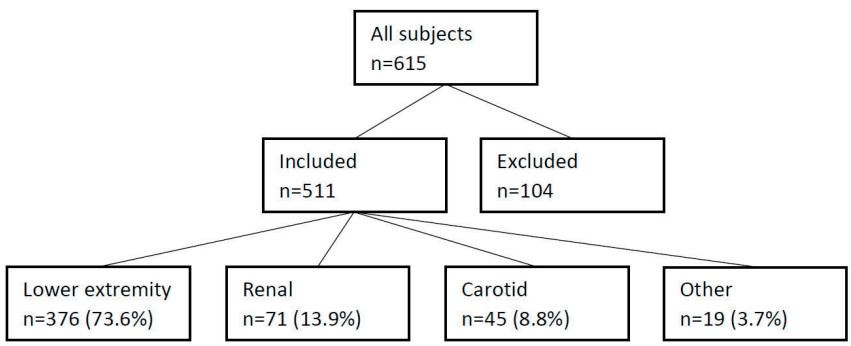

Figure 6.

Patients included in study I grouped according to differnet localization of PAD.

Statistical analysis

Data were expressed as mean (standard error [SEM]). Kruskall-Wallis test was used to evaluate differences in continuous variables between groups. If significant, the difference between two groups was tested by the Mann–Whitney U test. The Chi^2 test was used to evaluate differences in nominal variables between groups. Logistic regression analysis was performed including all variables differing between groups. Correlations between different variables were tested with Spearman's rank correlation coefficient.

Study II

Between 2010 and 2011, all men born in 1945-1946 (n=8269, figure 7) from the city of Malmö and 15 neighboring municipalities in the south-western part of the County of Skåne were invited to AAA screening.

All men were screened with ultrasound, and if not possible, CT was done (1.1%). AAA was defined as ≥ 30 mm.

We compared compliance to AAA screening between the Malmö and its 15 neighboring municipalities. Since Malmö was the largest municipality in the County of Skåne, we subdivided it into 10 different districts according to the previous administrative division of the city.

Socioeconomic background data were collected from Statistics Sweden and the municipal of Malmö, and were then related to compliances and prevalence for each district or municipality.

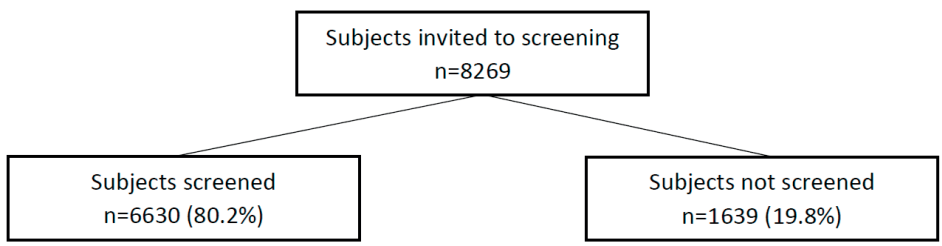

Figure 7.

Subjects invited to screening and grouped according to attendance to AAA screening in study II.

Comments

Since the study was published the City administration in Malmö has changed the previous 10 districts to only 5.

Statistical analysis

The Kruskall-Wallis test was used to evaluate differences in continuous variables between groups. Correlations between different variables were tested with Spearman's rank correlation coefficient. Logistic regression analysis was performed including all variables differing between groups.

Study III

In study III we identified the four municipalities with the lowest screening compliance in 2010-11. Based on these results from paper II, Landskrona and Hörby were allocated to be intervention municipalities, whereas Svalöv and Burlöv were chosen as controls (figure 8).

During 2013, all men born 1948 from the municipalities of Landskrona (n=190) and Hörby (n=102) received individually tailored invitations to the screening facilities at the Department of Vascular Diseases, Skåne University Hospital, Malmö for AAA screening.

Men born 1948 from the two control municipalities Burlöv (n=101) and Svalöv (n=79) received the same standard invitations from the public health system that has been used since the screening started in 2010, including a reminder to subjects not attending screening after the first invitation.

In collaboration with an internationally renowned advertising agency (The Fan Club, Malmö and Stockholm, Sweden), we developed a tailored screening invitation. The invitation package (figure 9) consisted of one envelope containing an invitation sheet with date, time, location for the screening appointment, and an individual detailed travel map showing the way from each subject's home to our screening facilities. The information sheet about the screening procedure and about AAA was also modified. The invitation also included a silver package containing a red tie with a knot tied like an aneurysm with a tag saying "Congratulations, this year is your 65th birthday, and this is a gift from Skåne University Hospital". The total cost of the intervention was 15850 €. All invitations were in Swedish but contained a referral in English to a webpage for multilingual information (English, Spanish, Dari, Turkish, Persian, Somali, Arabic, Polish, Finnish and Serbo-Croatian). The invitations were sent one

month prior to the screening appointment. If the invited men did not attend screening after the first invitation, a reminder was sent. The men were free to reschedule the appointment. Furthermore, an investigator (MZ) tried to contact all men in the intervention municipalities not attending screening by telephone.

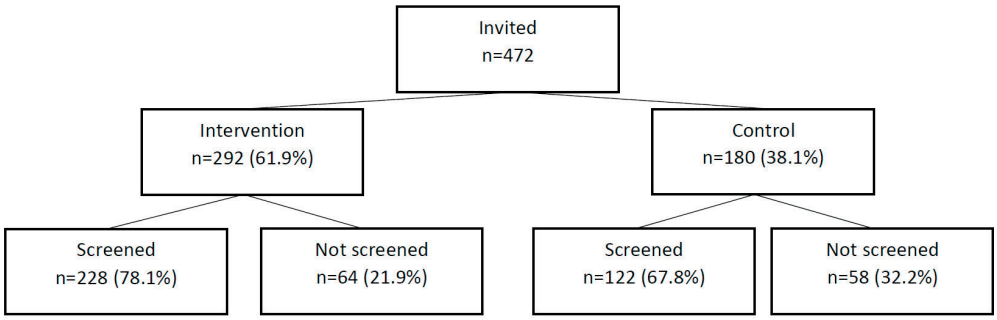

Figure 8

Distribution of subjects according to intervention group or control group and compliance (%) in study III.

Figure 9

The invitation package (silver package) containging a red tie (symbolizing an aneurysm) and the travel map.

Statistical analysis

Chi Square test was used for categorical data to evaluate difference between groups. Correlations between different variables were tested with Spearman's rank correlation coefficient. SPSS® (SPSS inc, IBM, New York, USA) software version 20 was used for the statistical calculations. A p-value <0.05 was considered significant.

Study IV

As this study is a Markov cohort simulation model, no real individuals were used. As input data, we used variables from the 19574 65 year-old-men invited to the Malmö AAA screening, of whom 15327 were screened between September 2010 and June 2014.

We developed a deterministic cohort model to evaluate the cost-effectiveness of AAA screening in 65-year old men. The model used different Markov health states to simulate the development and progression of AAA (Figure 10).

Two identical cohorts of 65-year-old men are simulated; the first cohort is invited to screening while the second is not. The cohorts are simulated for 35 years (to age 100 years).

The model contains 11 Markov health states, including no AAA, six AAA states, two post-surgery states, and two states for death (Figure 10).

The input data was mainly our own. If Malmö data was lacking, we used figures from the Swedvasc registry. If there were no Swedish data either, we used figures published in international literature.

Health gains were measured as QALY, and discounted at a yearly discount rate of 3% following Swedish recommendations.

The cost-effectiveness of AAA screening in 65-year-old men was evaluated by calculating an incremental cost-effectiveness ratio (ICER) for screening compared to no screening:

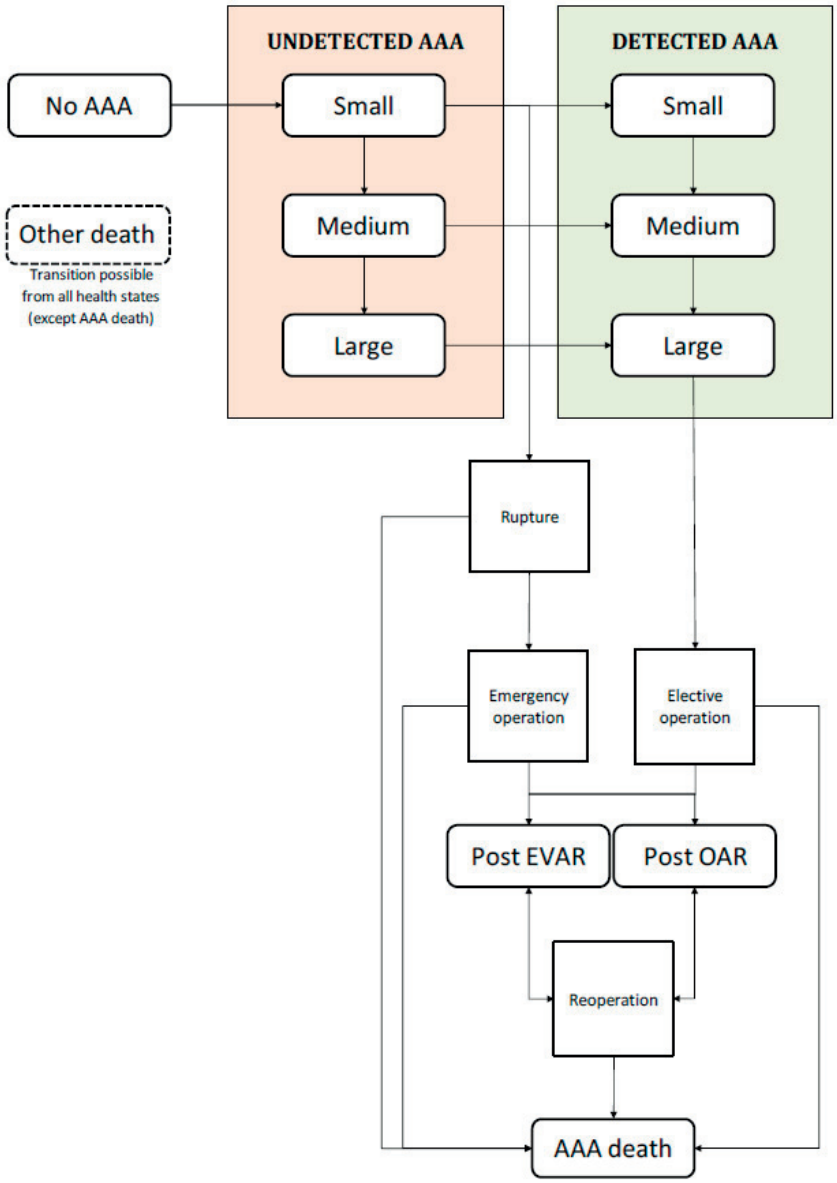

Figure 10

The Markov model used to evaluate screening for AAA. Rectangles represent health states and squares represent events. Possible transitions are represented by thin arrows. (OAR=open aortic repair.)

Statistical analysis

The face validity of the model was evaluated during its development by consulting with clinical experts. The model was also carefully tested and debugged in order to reveal any errors in logic or programming. Three different analysis were done, a base-case analysis, an analysis of medical optimization, and a sensitivity analysis.

Results

Study I

Mean APC-PCI complex levels were significantly higher in patients with AAA compared to controls (0.31 vs. 0.19 μg/L; P= 0.025). No differences concerning APC-PCI complex could be shown between patients with involvement of different anatomic vascular beds (P=0.743).

Importantly, 68/511 (13%) AAA were found in patients with PAD, more commonly (P<0.001) in men (56/282[20%] than in women (12/229[5%]). Of these 68 aneurysms, 8 (12%) needed immediate repair.

AAA and the APC-PCI complex

APC-PCI complex levels were higher (0.40[0.45] vs. 0.30[0.49] μg/L; P = 0.004) in patients with AAA. This difference persisted in multivariate analysis (P = 0.029). APC-PCI complex levels correlated positively with aortic diameter (P =0.012). In multivariate analysis only BMI (P = 0.001), gender (P = 0.001), age (P = 0.022), F–P-glucose (P = 0.007), and APC-PCI complex levels (P = 0.029) differed significantly between patients with and without AAA.

APC-PCI complex as a screening marker

A threshold value of ≥0.15 μg/L for the APC-PCI complex showed a specificity of 11%, a sensitivity of 97%, and a negative predictive value (NPV) of 96% for an AAA diagnosis. A receiver operating characteristic (ROC) curve for APC-PCI complex and AAA showed an area under the curve (AUC) of 0.610, (standard error [SE] 0.036, 95% confidence interval [CI] 0.539-0.680, P= 0.004, figure 11).

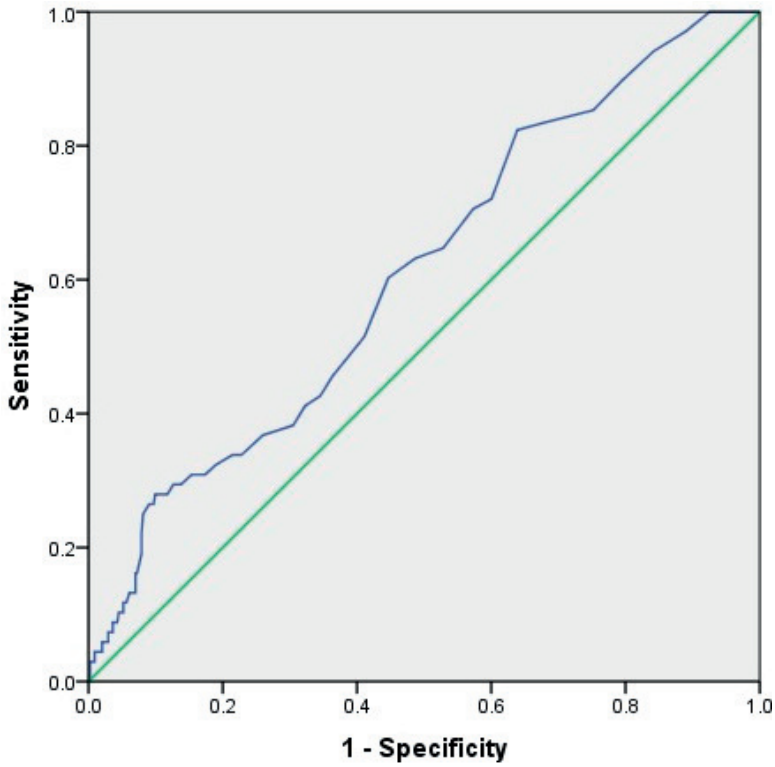

Figure 11.

ROC curve for APC-PCI complex as a screening marker for AAA.

Survival during follow-up

The survival rate during 4.8(0.5) years of follow-up was 67% (n = 341). Importantly, APC-PCI-levels did not differ between survivors and non-survivors.

Study II

Compliance

Compliance with screening in the entire area comprising 16 municipalities was 6630/8269 (80.2%). However, figures varied between 64.4% and 89.3% in different municipalities (P < 0.001). (Figure 12).

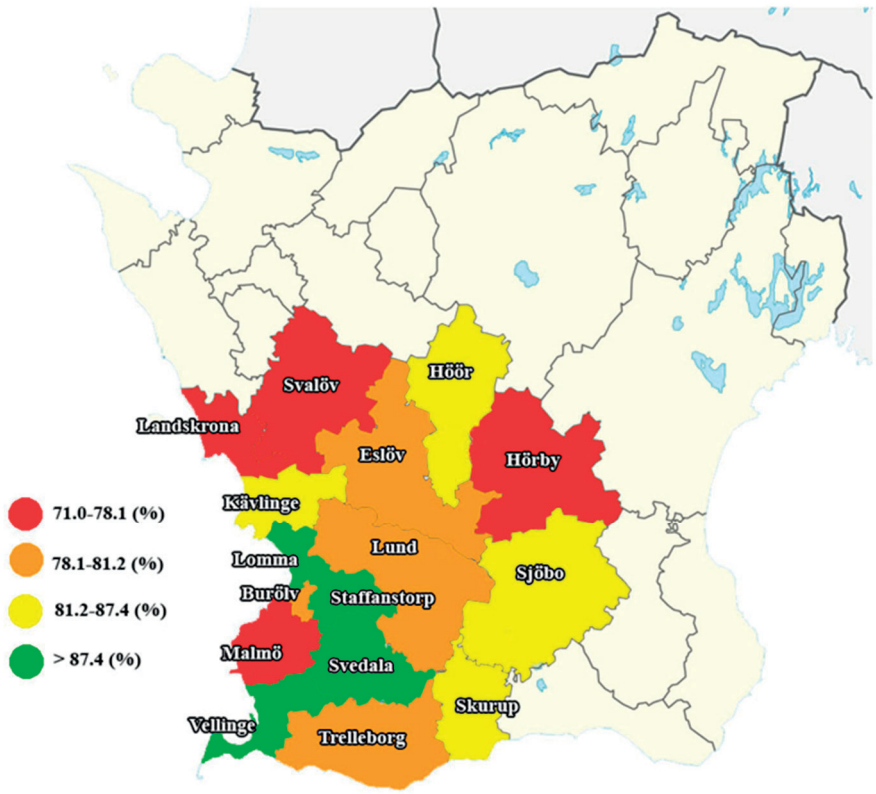

Figure 12.

Compliance (%) with screening in the entire area comprising 16 municipalities. Muncipalities are coded by colours based on interquartile range (IQR).

Compliance was significantly related to background variables in the different municipalities, such as mean income (r = 0.873; P < 0.001), percentage of subjects on welfare support (r = 0.698; P = 0.004), and proportion of immigrants (r = 0.685; P = 0.005).

On the other hand, compliance was not significantly related to distance to the screening site (r = 0.259; P = 0.333), unemployment rate (r = 0.247; P = 0.375), proportion of subjects with higher education (r = 0.496; P = 0.060), or smoking rates (r = 0.132; P =0.625).

In the city of Malmö, compliance differed between the 10 administrative parts (P= 0.002) (Figure 13) and was related to background variables in the different districts such as mean income (r = 0.948; P < 0.001), unemployment rate (r = 0.796; P = 0.006), distance to the screening site (r = 0.760; P = 0.011), and proportion of immigrants (r = 0.650; P =0 .042). On the other hand, compliance was not related to smoking (r = 0.565; P = 0.089), percentage of subjects on welfare support (r = 0.431; P =0.214), or proportion of subjects with higher education (r = 0.015; P = 0.967). When compliance was related to all different socioeconomic variables in multivariate analyses, the significant correlations found with different individual socioeconomic variables disappeared.

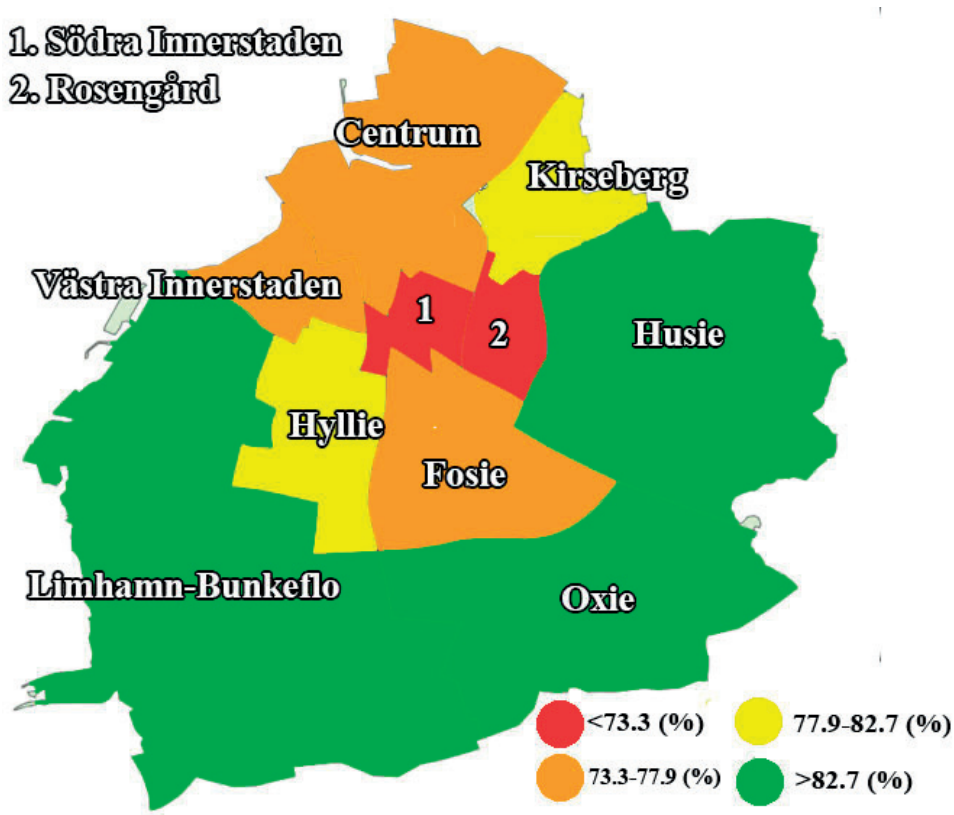

Figure 13.

Compliance (%) with screening in the 10 administrative parts of Malmö. The 10 adminstrative parts are coded by colours based on IQR.

Prevalence

A total of 117 AAAs (1.76%) were detected. The number of AAAs in the different municipalities are shown in figure 14, and the number of AAAs in the 10 different districts in Malmö in figure 15.

AAA prevalence differed between the 16 municipalities (P =0.003). The prevalence of screening detected AAAs was not significantly related to background variables in the different municipalities such as mean income (r = 0.118; P =0.676), percentage of subjects with higher education (r = 0.387; P = 0.154), proportion of immigrants (r = 0.347; P = 0.206), unemployment rate (r =0.192; P =0.492), proportion of subjects on welfare support (r =0.065; P =0.817), or smoking rate (r =0.204;P =0.450). In the city of Malmö, the prevalence of screening detected AAA differed between the 10 administrative areas (P =.020) and was significantly related to background variables in the different districts such as smoking rate (r =0.784; P =0.007), unemployment rate (r =0.783; P =0.007), mean income (r =0.754; P =0.012), and proportion of immigrants (r =0.644; P =0.044), but not to the percentages of subjects with higher education (r =0.404; P =0.247), or welfare support (r =0.462; P =0.179). When AAA prevalence was related to all different socioeconomic variables in multivariate analyses, the significant correlations found with different individual socioeconomic variables disappeared.

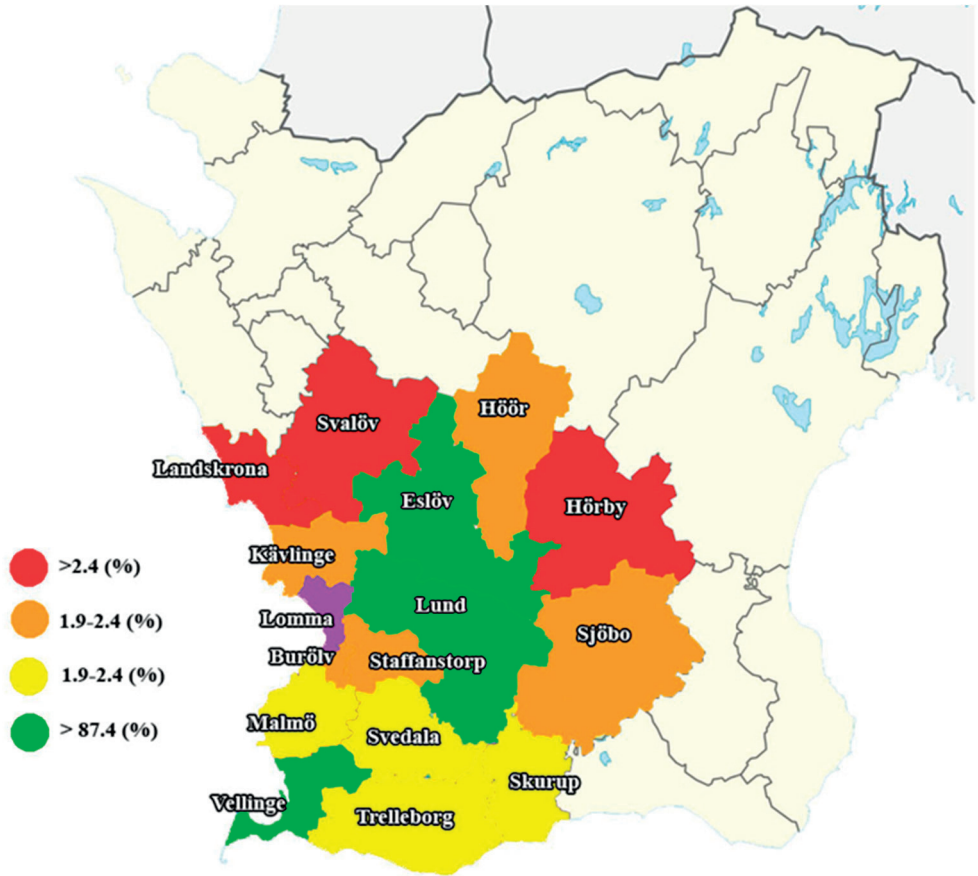

Figure 14.

Prevalence (%) of AAA in the entire area comprising 16 municipalities. Muncipalities are coded by colours based on IQR.

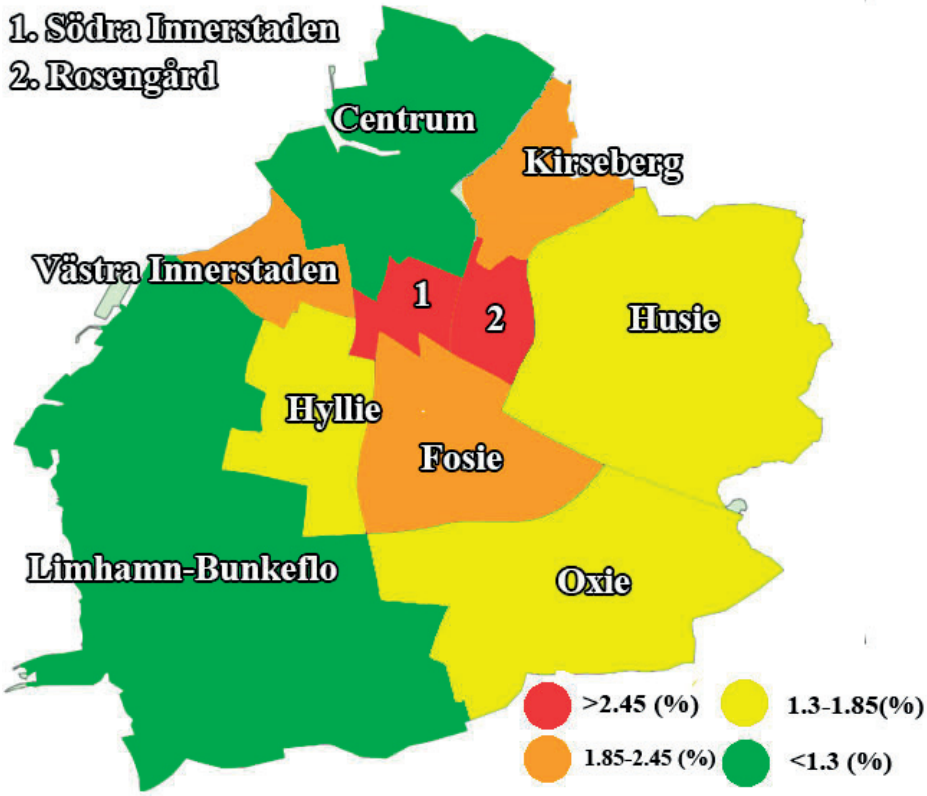

Figure 15.

Prevalence (%) of AAA in the 10 administrative parts of Malmö. The 10 adminstrative parts are coded by colours based on IQR.

Study III

Overall screening compliance in the four municipalities in 2010–12 before intervention was 72.9%. Compliance in the two intervention municipalities increased from 71.4% in 2010–12 to 78.1% in 2013, which was significantly higher (OR 1.7; 95% CI 1.1–2.6; p=0.013) than in the two control municipalities, where it remained unchanged (75.5% in 2010–12 and 67.8% in 2013) (Tables 1- 2)

Intervention	2010-2012	2013	p (2010-12 vs. 2013)
Landskrona	506/732 (69.1)	144/190 (75.8)	0.073
Hörby	172/217 (79.3)	84/102 (82.4)	0.518
Total	678/949 (71.4)	228/292 (78.1)	0.025
Control			
Svalöv	199/271 (73.4)	52/79 (65.8)	0.186
Burlöv	218/281 (77.6)	70/101 (69.3)	0.098
Total	417/552 (75.5)	122/180 (67.8)	0.040

Table 1. Compliance with AAA screening before (2010-2012) and after (2013) intervention in control and intervention municipalities (n attending / n invited [%]).

	2010-2012	p	2013	p (intervention vs control)
Intervention	678/949 (71.4)	0.298	228/292 (78.1)	0.013
Control	417/552 (75.5)		122/180 (67.8)	

Table 2. Comparison of compliance with AAA screening in intervention and control municipalities before (2010-2012) and after (2013) intervention (n attending / n invited [%]).

Study IV

Base-case analysis

The incremental cost of the screening strategy compared with no screening were €169 per person and year. Incremental gain per subject in the screened cohort was 0.011 QALY, corresponding to an ICER of €15710 per QALY. The undiscounted life years were 18.550 versus 18.529 with a difference of 0.021

Medical optimization

All patients diagnosed with an AAA received secondary medical preventive treatment. Assuming a 5% reduction in all-cause mortality, the incremental cost of screening was €173 per person and year. The incremental gain per subject in the screened cohort was 0.012 additional QALY, corresponding to an ICER of €14886 per QALY.

However, when assuming a 10% risk reduction, the incremental cost of screening was €175 per person and year. The gain per subject in the screened cohort was 0.013 additional QALY, corresponding to an ICER of €13922 per QALY.

Sensitivity analysis

The sensitivity analysis indicated that results from the base case analysis were robust. The lowest ICER of €9989 per QALY was found when the cost of ultrasound was lowered to € 16.45, and the highest ICER of €22979 when rupture risk of large AAA was lowered to 10%. Most of the other sensitivity analyses had limited effect on the results. The ratio between EVAR and OR for example did not significantly change the ICER.

Discussion

AAA is a hideous life threatening disease that most often is asymptomatic until it ruptures. rAAA is a painful and serious predicament with a mortality of 80-90%.[233] Half of the patients die before arriving to hospital, leaving family members in sorrow and shock. In Sweden about 700-1000 patients die each year due to rAAA, corresponding to 1.5% of all deaths in men.[234]

Four randomized trials[102-105] have shown that screening for AAA is cost-effective to reduce both AAA related mortality by 50% and all-cause mortality by 3%.[134] These trials have been the reason why screening 65 year-old-men for AAA has been introduced in Sweden.

Our four studies I-IV all evaluated AAA screening from different point of views. In study I, we tried to establish if it was possible to use a biological marker as a screening tool. Importantly, this study was also in a sense a targeted screening for AAA in patients with peripheral arterial disease (PAD). In Study II we evaluated our own screening concerning compliance and prevalence, and how these entities were affected by background SES. After identifying areas with low compliance to AAA screening in study II, we tried on study III to increase compliance in those areas. Finally in study IV, after having noted the low prevalence of AAA in study II, we evaluated if screening for AAA, is still cost-effective in our own screening center where all patients with AAA receive secondary preventive medical treatment and all patients with large aneurysms are operated with the new EVAR technique.

It is known that patients with PAD have higher prevalence of AAA compared to healthy controls.[235] The relationships between AAA and cardiovascular events such as stroke and acute coronary syndrome are well established[70,172]. Our finding in study I that 13% of a Swedish population with PAD have concomitant AAA, is important in the context of screening and secondary preventive medical treatment. Firstly, there is an ongoing discussion concerning targeted screening. As patients with PAD certainly have a high AAA prevalence, screening hence has the potential to be cost-effective in this group. However since this group of patients were older (70[12] years in our study) and more frequently have comorbidities, this cost-effectiveness might as well be less since the life expectancy is decreased due to death of other causes than AAA. Nevertheless, 8 (12%) of the men found to have AAA needed immediate AAA repair. Interestingly enough, women with PAD had a 5% prevalence for AAA. Targeted screening for women with PAD might therefore perhaps as well be cost-effective.

Another Swedish study by Svensjö et al showed that the prevalence of AAA in 70-year-old women was 0.03% among never smokers and 2.2% among current smokers.[106] Secondly, since most patients with PAD at our center are already treated with statins, ASA, and blood pressure lowering drugs, the AAA diagnosis caused no further addition to their secondary preventive treatment. Thirdly, APC-PCI complex as a screening method was not sensitive enough to be used as a biological marker for AAA. Nevertheless, the negative predictive value (NPV) was 96%, in other words, if the result was negative it was highly unlikely to find an AAA. Maybe we could use APC-PCI complex in the clinical setting in both men and women with PAD; in case of a negative result no further imaging of the aorta is necessary. In conclusion, screening for AAA in patients with PAD should be considered.

The overall compliance to AAA screening in Malmö (80%) should be compared to figures reported from Uppsala (85%)[236] and Stockholm (78%).[109] These compliance figures from AAA screening programs are well comparable to those from other screening programs in Sweden such as for breast (75-85%)[237], colorectal (39%)[238], and cervical cancer (55%).[239] More importantly, it should be mentioned that the lower compliance seen in breast cancer screening could be due to the fact that invited women are offered new possibilities to be screened another year if not attending when invited. However, we noticed that compliance varied between 64% and 89% in different areas, and that low compliance was related to background area socioeconomic variables such as low income, higher percentages on welfare support, higher proportions of immigrants, and unemployment rates. Similar findings have also been shown in Stockholm concerning AAA screening.[109]

The prevalence of AAA was higher in regions with low compliance to screening, and prevalence of screening detected AAA was related to background area socioeconomic variables such as smoking, unemployment, income, and proportion of immigrants. The fact that subjects not attending screening programs have both higher prevalence of the disease, and lower SES has been reported earlier. [240-241] An explanation for this may be that immigrants tend to settle in areas already occupied by other immigrants. This leads to segregation and a mistrust towards institutions. If immigrants do not master the native language, they will experience difficulties in achieving higher education and employment, resulting in lower income. People with jobs generating higher income tend to move to areas of higher SES, where the citizens are more informed concerning health issues. Compliance to AAA screening in our district was related to low income, higher percentages of immigrants, unemployment, and welfare support; variables reflecting that compliance is lower for economically poor citizens. Therefore, it would be interesting to see the effect on compliance if the fee for screening was removed. When the screening fee for breast cancer was abolished in Stockholm, compliance increased in areas with previously low compliance.[242]

In an attempt to disseminate our findings, we held a press conference in an area with low compliance and gave interviews on both regional and Swedish national radio stations.

The important findings in study II were the reasons for our attempt to increase compliance in areas with low compliance together with a professional advertising agency. To our present knowledge, our study is the first to show that AAA screening compliance can be increased by collaboration with an advertising agency. Methods that have previously been used to increase compliance are reminders and telephone consulting.

Compliance in the two intervention municipalities increased significantly from 71% to 78%, whereas figures were unchanged in the control areas. Interestingly, it is possible to increase compliance to AAA screening in low compliance areas without reducing the screening fee.

As mentioned earlier, several RCT have shown that screening for AAA is cost-effective.[102-105] These trials were conducted in areas with higher prevalence, and as prevalence in Malmö (1.8%) as well as in other parts of Sweden is much lower, we wanted to evaluate the cost-effectiveness (study IV) of our AAA screening. Furthermore, subjects undergoing AAA interventions at our vascular center are predominantly (96%) treated with EVAR, and almost all patients with AAA receive antiplatelet treatment, statins, and blood pressure lowering medication (if hypertensive). Several health-economic models of AAA screening have been presented during the last years, but none of these has taken the triad of low prevalence, high frequency of EVAR, and secondary preventive medication into consideration.

In our base-case analysis the incremental cost-effectiveness ratio (ICER) was €15710 per QALY. Assuming a 10% reduction of all-cause mortality, the ICER decreased to €13922 per QALY. It therefore seems justified to continue AAA screening in Malmö, since the Swedish National Board of Health and Welfare has accepted the Swedish breast cancer screening as cost-effective at a cost of € 11 968-39 180 per QALY, depending on screening age.

Future perspectives

Compliance to AAA screening

The mechanisms behind low compliance to a screening program are complex and challenging. In order to maintain and increase compliance with AAA screening, it is important to evaluate important mechanisms in other screening programs. Collaboration with the private sector enables new insights not possible to obtain from the public health care sector. We are currently negotiating with an advertising agency to update the AAA screening invitation in the whole region. In the future, 65 year-old-men invited to screening will be more apt to use multimedia. With future additional help from internet and smartphone applications, compliance might be increased further. A computer application for AAA-screening is currently under development at our institution.

Prevalence of AAA

The prevalence of AAA was previously higher in Sweden compared to nowadays.[85] Presently, Swedish men have lower prevalence of AAA compared to many other countries.[248,97] The reason for this change is most likely the decreasing smoking rates in Sweden. On the other hand, AAA prevalence is known to be low in Asians and Afro-Americans. According to a recent study[249] from Japan, however, the prevalence of AAA seems to increase. In the future, the countries with the highest prevalence of AAA might be those with increasing smoking rates. If some countries in the future will prohibit smoking, potential effects of this on prevalence of AAA will be most interesting to evaluate.

Medical therapy

The result from ongoing trials concerning pharmacological possibilities to prevent growth and rupture of AAA will be very important. If medical treatment can reduce all-cause mortality through protection from cardiovascular events, screening for AAA

will be even more cost-effective since each patient screened will gain more healthy life years.

Areas of uncertainty

We still do not know if potential future epidemiological changes such as in smoking habits, life expectancy, or efficiency of surgery will change the conditions for screening AAA screening in women. Neither do we know if screening should be offered to selected subgroups only, as for example to smokers.

Furthermore, uncertainty still prevails concerning whether subjects with sub-aneurysmal aortas of 25-29 mm diameter should be included in the follow-up protocol to prevent later AAA rupture.

We also have to examine if patients with sub-aneurysmal aortas benefit from the same secondary preventive medication as patients diagnosed with AAA.

Finally, potential psychological aspects of screening detected AAA for the patient and his family members need to be clarified.

Conclusions

- The use of APC-PCI complex as screening marker for the detection of AAA in patients with peripheral arterial disease was not sensitive enough to be used in a clinical setting (I).

- AAA prevalence and compliance to ultrasound screening for AAA differed between men from different geographical areas, and men from areas with low SES generally showed lower compliance and higher prevalence of AAA (II).

- Collaboration with a professional advertising agency increased the compliance to AAA screening (III).

- AAA screening is still cost-effective in the new era of decreased AAA prevalence, EVAR as the predominant treatment method, and improved medical treatment (IV).

Populärvetenskaplig sammanfattning på svenska (Comprehensive summary in Swedish)

Stora kroppspulsådern är det centrala kärl som från hjärtat leder blodet vidare till kroppens alla organ. När kroppspulsåderns kärlvägg försvagas resulterar detta i en utvidgning (bråck). Ett kroppspulsåderbråck sitter vanligtvis i nivå med naveln, strax nedom kärlen som försörjer njurarna. Förekomsten av kroppspulsåderbråck är 1.8% hos 65 åriga män. Män drabbas 4-6 gånger oftare jämfört med kvinnor. Med tiden kan bråcket bli större vilket ökar risken för att det spricker, ledande till att blodet som pumpats ut ifrån hjärtat istället rinner utanför kärlet ut i bukhålan. Ofta är den drabbade helt ovetande om sjukdomen som vanligtvis inte ger symtom förrän bråcket spricker. Då detta sker dör nästan 50% innan de kommer till sjukhuset, och endast 33% kan genomgå kirurgi. Totalt är dödligheten vid sådan händelse 80-90%. Fyra stora studier har kunnat visa att man kan halvera dödligheten i spruckna pulsåderbråck genom att med hjälp av ultraljud screena 65 åriga män och operera bråck över en viss storlek i förebyggande syfte. På denna indikation har man introducerat screening av stora kroppspulsådern hos alla 65 åriga män i Sverige.

Denna avhandling har studerat olika aspekter av screening för kroppspulsåderbråck.

Studie I: Syftet var att studera om en biologisk markör i blodet (APC-PCI komplex) kan användas för att med hjälp av ett blodprov kunna screena för kroppspulsåderbråck hos patienter med kärlsjukdom inom andra kärlområden men utan känt kroppspulsåderbråck. Studien visade att det inte gick att använda denna markör eftersom dess känslighet var otillräcklig. Däremot upptäckte vi att förekomsten av kroppspulsåderbråck var hög (13%) hos en sedan tidigare kärlsjuk population.

Studie II: Syftet var att kartlägga hur hörsamheten till screening och förekomsten av kroppspulsåderbråck påverkades av olika socioekonomiska faktorer. Vi upptäckte att hörsamheten till screening varierade stort beroende på i vilket geografiskt område männen bodde. Vi noterade att områdena med lägst hörsamhet till screening hade högre förekomst av invandrare, lägre utbildning och högre arbetslöshet. Förekomsten av kroppspulsåderbråck var även högre i de områdena där hörsamheten var som lägst.

Med andra ord; de patienter som löpte störst risk att vara sjuka kom inte till vår undersökning.

Studie III: Syftet var att försöka förbättra hörsamheten i de områdena där denna var som lägst. Detta gjorde vi genom att samarbeta med en professionell reklambyrå. Reklamfirman tog fram en förbättrad kallelse till männen som genomgått språklig redigering, fått ändrad layout, samt kompletterats med karta med vägbeskrivning ifrån deras hem till vår screeninglokal samt en röd slips knuten som ett kroppspulsåderbråck. Resultatet var att hörsamheten ökade märkbart i de områdena där vi använde materialet från reklamfirman.

Studie IV: Syftet var att med hjälp av datasimulering utvärdera om det fortfarande är kostnadseffektivt att screena 65 åriga män för kroppspulsåderbråck när förutsättningarna har ändrats. De nya förutsättningarna vi ville undersöka var den lägre förekomsten av kroppspulsåderbråck, det faktum att majoriteten av kirurgin görs med hjälp av kateterburen protesinläggning i aorta samt att alla patienter erhåller sekundärpreventiv medicinering. Undersökningen visade att det fortfarande är konstnadseffektivt att screena 65 åriga män för kroppspulsåderbråck.

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Paper I

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APC-PCI complex levels for screening of AAA in patients with peripheral atherosclerosis

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Abstract To evaluate the use of activated protein C–protein C inhibitor (APC-PCI) complex levels for detection of abdominal aortic aneurysm (AAA) in patients with peripheral atherosclerotic disease (PAD). APC-PCI levels and aortic diameter evaluated in 511 PAD patients without previously known AAA followed-up concerning survival for 4.8(0.5) years. AAA was found in 13 % of patients. Aortic diameter correlated ($r = 0.138$; $p = 0.002$) with APC-PCI levels which were higher (0.40[0.45] vs. 0.30[0.49] μg/l; $p = 0.004$) in patients with AAA. This difference persisted in multivariate analysis ($p = 0.029$). A threshold value of APC-PCI ≥0.15 μg/L showed a specificity of 11 %, a sensitivity of 97 % and a negative predictive value of 96 % for an AAA diagnosis. APC-PCI levels were higher in patients with AAA, and showed high sensitivity but low specificity for the diagnosis and can therefore not be considered as a screening tool in PAD patients. An AAA prevalence of 13 % in patients with PAD indicates a need for AAA screening within this population.

Keywords Activated protein C · Protein C inhibitor · Atherosclerosis · Aortic abdominal aneurysm · Blood coagulation · Screening

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Introduction

Background

An abdominal aortic aneurysm (AAA) is found in 1.7–6 % of 65 year old men [1, 2], with the lower figure found in more recent studies [2]. Men outnumber women by approximately 4:1 among AAA patients, and rupture of AAA is the tenth leading cause of death in older men [3]. Screening for AAA among men aged 65–74 is rapidly gaining popularity in many countries as it has been shown to be a highly cost effective and valuable tool for reduction of AAA related mortality [4, 5]. Such calculations have been based on older studies with higher AAA prevalence [4] however.

Even if the prevalence of AAA is higher in patients with atherosclerotic disease than in the general population [6, 7], there is yet no worldwide consensus to screen patients with established atherosclerotic disease for the presence of AAA [8].

Several studies have indicated the importance of blood coagulation for the pathogenesis of atherosclerotic disease. Markers of coagulation are both elevated and related to the severity of disease in patients with atherosclerotic disorders [9–14]. One such marker of coagulation that has recently gained much interest is the activated protein C (APC)–protein C inhibitor (PCI) complex [15].

APC is an important anticoagulant that inhibits the action of factors Va and VIIIa as cofactors in the formation of thrombin and factor Xa respectively. Protein C, a serine protease, is activated by a complex between thrombin and an endothelial membrane protein called thrombomodulin. The activity of APC is downregulated by the serpin PCI which acts by forming an APC-PCI complex, thus rendering APC inactive.[16, 17] Since APC is formed solely

by the action of thrombin, the amount of APC-PCI complex correlates directly to the rate of thrombin generation and coagulation activation [15]. The APC-PCI complex is a marker of increased coagulation activation in myocardial infarction, deep vein thrombosis and various other thrombotic disorders [18–20]. Previously used methods for measuring the APC-PCI complex have not been accurate and simple enough for use in clinical practice, however. Strandberg et al. have developed a sensitive immunofluorometric sandwich assay specific for the complex bound form of PCI [21]. Using this method APC-PCI complex levels have been found to be triplefold increased in AAA-patients [14, 21, 22], and therefore the use of the APC-PCI complex as a screening biomarker has been considered. However slightly increased APC-PCI levels have also been observed in coronary artery disease [20, 23], venous thromboembolism [18, 24], and in peripheral arterial disease (PAD) [14].

The prevalence of AAA has also been reported to be increased in PAD patients [5, 7]. As APC-PCI levels correlate to aneurysm diameter [24], they might perhaps be valuable for detection of this disease. The aim of the present study was to evaluate if APC-PCI complex levels can be used as a screening marker for AAA among consecutive patients without previously known AAA hospitalized for PAD.

Materials and methods

Population

We enrolled 511 consecutive patients (age 70[12] years) hospitalized for PAD in the lower extremity ($n = 376$), renal ($n = 71$), carotid ($n = 45$) or other peripheral (visceral or upper extremity, $n = 19$) arteries without previously known AAA, at the Vascular Centre, Skåne University Hospital Malmö, Sweden, between September 2004 and August 2007. Patients with acute cardioembolic events were not included.

A healthy group of 219 age and sex-matched individuals (median age 68, range 53–80, 181 males and 38 females) from the Malmö Prevention Project [25] without symptomatic atherosclerosis or known AAA were used as controls. Antiplatelet therapy was used by 24(11 %), statins by 23(11 %), and blood pressure lowering drugs by 57(26 %) controls.

Methods

In all cases APCI-PCI Complex samples were drawn on all patients before any diagnostic imaging, invasive vascular diagnostic, or interventional procedure was undertaken. The investigators were blinded to the result of AAA assessment prior to the below outlined laboratory analysis of APC-PCI levels. Samples were collected in 5-mL vacuum tubes (Stabilyte®, Biopool, Umeå, Sweden) containing citrate with a low pH, thus precluding APC-PCI complex formation in vitro [26].After centrifugation the plasma was frozen at −70 °C for later analysis of the APC-PCI complex concentration with the sandwich assay developed by Strandberg et al. [21].

Patients treated with warfarin <4 weeks prior APC-PCI sampling were excluded ($n = 104$) from the study as warfarin interacts with the synthesis of the vitamin K dependent protein C. Antiplatelet therapy was used by 505(98 %), statins by 455(89 %), and blood pressure lowering drugs by 388(76 %) included patients.

We collected data from the medical computer based records systems Melior® (Siemens AG, Munich, Germany), and PASIS® (comForte GmbH, Wiesbaden, Germany) concerning systolic and diastolic blood pressures, b(blood)-hemoglobin, b-leukocytes, C-reactive protein (CRP), p(plasma)-creatinine, p-total cholesterol, p-triglycerides, p-high density lipoprotein cholesterol, p- low density lipoprotein cholesterol, fp-glucose, body mass index, medication, presence of diabetes mellitus, and smoking habits at the time of sampling.

Data on the maximal infrarenal aortic diameter in all 511 patients was retrieved from SECTRA PACS® (Sectra Imtec AB, Linköping, Sweden). The different objective imaging modalities used for diameter evaluation were ultrasound (US), computer tomography (CT), magnetic resonance imaging (MRI) and conventional angiography. Evaluations were performed in conjunction with APC-PCI-sampling. With CT or MRI the infrarenal aorta was measured from outer wall to outer wall at the largest diameter, whereas with US the largest infrarenal anteroposterior diameter was measured according to the principle “leading edge to leading edge” [27]. An AAA was defined as an infrarenal aortic diameter of 3 cm or larger [1]. An AAA found by US was not re-evaluated by CT or MRI unless clinically indicated. The thoracic aorta was not evaluated in our study since thoracic aortic aneurysms are rare compared to AAA [28].

Patients were followed up for 4.8 (0.5) years concerning survival, assessed from the Swedish population registry.

Statistics

Data were expressed as mean (standard error [SEM]). Kruskall-Wallis test was used to evaluate differences in continuous variables between groups. If significant, the difference between two groups was tested by the Mann–Whitney U test. The Chi [2] test was used to evaluate differences in nominal variables between groups. Logistic

regression analysis was performed including all variables differing between groups. Correlations between different variables were tested with Spearman's rank correlation coefficient. SPSS® (SPSS inc, IBM, New York, USA) software version 18 was used for the statistical calculations.

Ethical considerations

All patients gave written consent to participation and the study was approved by the ethics committee of Lund University.

Results

Mean APC-PCI complex levels in patients were higher compared to the control group (0.31 vs. 0.19 μg/L; $p = 0.025$). There were no significant differences concerning APC-PCI complex levels between patients with atherosclerosis in the lower extremity, renal, carotid, or other arteries ($p = 0.743$). An AAA was found in 68/511 (13 %) patients (43 with atherosclerosis in lower extremity arteries, 11 in renal, 7 in carotid, and 7 in other peripheral arteries), more commonly ($p < 0.001$) in men (56/282[20 %] than in women (12/229[5 %]). Of these 68 aneurysms, 8 (12 %) needed immediate repair.

AAA and the APC-PCI complex

APC-PCI levels were higher (0.40[0.45] vs. 0.30[0.49] μg/l; $p = 0.004$) in patients with AAA. This difference persisted in multivariate analysis ($p = 0.029$).

APC-PCI complex levels were 0.30(0.18) μg/l in patients with AAA 30–39 mm, 0.46(0.35) μg/l in patients with AAA 40–49 mm, 0.78(0.78) μg/l in patients with AAA > 50 mm; ($p = 0.012$). In Table 1 correlations with APC-PCI levels and aortic diameter are given.

In spite of the many significant correlations in univariate analysis, however, only BMI ($p = 0.001$), gender ($p < 0.001$), age ($p = 0.022$), F–P-glucose ($p = 0.007$) and APC-PCI complex levels ($p = 0.029$) differed significantly between patients with and without AAA in multivariate analysis.

The APC-PCI complex as a screening marker for AAA

A threshold value of ≥0.15 μg/L for the APC-PCI complex showed a specificity of 11 %, a sensitivity of 97 % and a negative predictive value (NPV) of 96 % for an AAA diagnosis. (Fig. 1) If a threshold of >0.2 had been selected, specificity would have increased to 36 %, sensitivity decreased to 82 %, and NPV decreased to 93 %.

Survival during follow-up

The survival rate during 4.8(0.5) years of follow-up was 67 % ($n = 341$, Table 2). Importantly, APC-PCI-levels did not differ between survivors and non-survivors. In multivariate analysis, however, b-hemoglobin ($p < 0.001$), age ($p = 0.013$) and HDL ($p = 0.029$) differed significantly between survivors and non-survivors.

APC-PCI complex levels did not differ between patients with ($n = 29$, 0.29[0.09] μg/L) and without ($n = 184$, 0.39[0.01] μg/L) stroke ($p = 0.730$), or between patients with ($n = 45$, 0.30 [0.02] μg/L) and without ($n = 168$, 0.31[0.04] μg/L) acute coronary syndrome ($p = 0.033$) during follow-up. Neither was there any significant difference ($p = 0.351$) if patients with either stroke, acute coronary syndrome or death during follow-up ($n = 170$, 0.38 [0.06] μg/L) were compared with those without any such event ($n = 341$, 0.28[0.01] μg/L).

Discussion

With the sensitive assay for quantification of APC-PCI levels [21, 29] used in this study, patients with AAA have previously been shown to have threefold higher APC-PCI complex levels compared with a control population [30], and APC-PCI complex levels have also been shown to correlate weakly with AAA size [24], whereas no correlations have been found between thrombus surface area or volume of AAA and levels of the APC-PCI complex [31]. However, it has also been shown that APC-PCI complex levels are increased in patients with atherosclerotic disease in both carotid [32] and lower extremity PAD manifesting itself as intermittent claudication or critical limb ischemia [24]. It was therefore relevant to evaluate if APC-PCI complex levels could be used in screening for patients requiring invasive PAD treatment.

We tried to establish a cut-off level of APC-PCI complex levels for AAA detection, and by using a value of ≥0.15 μg/L based on earlier control populations we missed only two patients with AAA in our population. For a cut-off level to be clinically relevant, however, a balance is needed between sensitivity and specificity. As the specificity of this APC-PCI complex level was low, it did not allow us to exclude a significant proportion of arteriosclerotic patients (only 74/511[14.5 %]) from the need of further screening.

As the negative predictive value is high, the APC-PCI complex value can still be of some use when patients with peripheral atherosclerosis are evaluated concerning screening for AAA, however, as low levels of the APC-PCI complex strongly indicates that the presence of an AAA is highly unlikely. Thus it is only in the relatively few

Table 1 Characteristics of 511 patients with peripheral arterial disease, with or without abdominal aortic aneurysm (AAA). Mean (SEM)

Variable	All patients ($n = 511$)	With AAA ($n = 68$)	Without AAA ($n = 443$)	p Value
Gender male/female	282/229	56/12	226/217	0.000
Age (years)	70(12)	73(8)	70(12)	0.04
Body mass index (kg/m^2)	25.6(4.5)	26.2(4.7)	25.5(4.5)	0.251
APC-PCI[a] (μg/L)	0.31(0.48)	0.40(0.45)	0.30(0.49)	0.004
Aortic diameter (mm)	23.8(7.5)	38.1(10.0)	21.6(3.7)	0.000
Systolic blood pressure (mm Hg)	148(24)	150(22)	148(24)	0.528
Diastolic blood pressure (mm Hg)	76(13)	79(15)	75(12)	0.079
B-hemoglobin (g/L)	133(17)	134(18)	133(17)	0.531
B-leukocytes ($\times$ 10^9/L)	8.4(3.1)	8.6(2.4)	8.4(3.2)	0.241
P–C-reactive protein (mg/L)	14(31)	22(42)	13(29)	0.007
P-creatinine (μmol/L)	115(108)	126(93)	113(110)	0.016
P-total cholesterol (mmol/L)	4.4(1.06)	4.5(0.98)	4.4(1.07)	0.653
F–P-triglycerides (mmol/L)	1.4(0.9)	1.5(1.0)	1.4(0.85)	0.502
P-high density lipoprotein (mmol/L)	1.3(0.4)	1.2(0.5)	1.26(0.4)	0.132
P-low density lipoprotein (mmol/L)	2.6(1.0)	2.7(0.9)	2.6(1.0)	0.392
F–P-glucose (mmol/L)	6.7(2.7)	6.3(1.0)	6.8(2.9)	0.545

B blood, *P* plasma, *F* fasting

[a] Activated protein C–protein C inhibitor complex

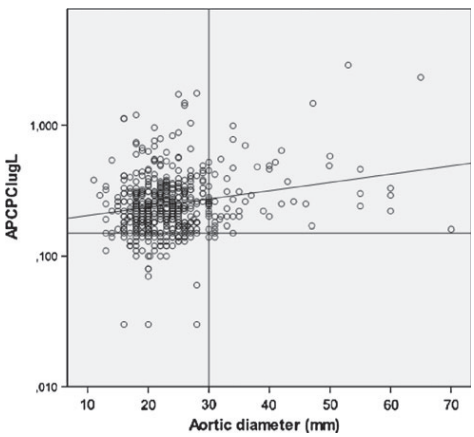

Fig. 1 Relationship between aortic diameter and levels of activated protein C–protein C inhibitor (APC-PCI) complex in 511 patients with peripheral arterial disease. (r = 0.138; $p = 0.002$). *Vertical line* definition of abdominal aortic aneurysm (30 mm), *horizontal line* cut-off level of 0.15 μg/L, *linear regression line* relationship between APC-PCI levels and aortic diameter

patients with low levels of the marker that the use of further screening procedures based on imaging can be omitted.

The usage of APC-PCI complex levels as a predictive marker for AAA among healthy 65-year old men screened for AAAin the general population is currently evaluated at our department.

Our study also confirmed the high prevalence of AAA among patients with peripheral atherosclerotic disease [6, 7].Our prevalence of 13 % is higher than previous Swedish figures in vascular outpatients [6], but the same as reported by Barba et al. [7] in a group of patients with lower limb atherosclerosis. AAA screening among patients of all age groups with established atherosclerosis might well be even more effective in reducing AAA mortality.

Furthermore, the AAA prevalence of 5 % in women in our study is higher than the 4 % prevalence of AAA in the male populations on which the scientific evidence for today's AAA screening in men is based. [32–35] Our findings therefore support the notion that it is reasonable to screen more actively for AAA among patients of both genders with atherosclerotic disease [7] of such dignity that hospitalization for evaluation of possible invasive treatment is considered indicated.

We found no significant relationships between APC-PCI complex levels reflecting thrombin activation and overall mortality in our patients with peripheral atherosclerosis.

Our study has several other limitations. As outlined in current guidelines for AAA diagnosis and treatment [8] several different imaging modalities were used for evaluation of aortic diameter in our patients. To save our patients from unnecessary radiation and contrast exposure, the method for determination of aortic diameter which was considered as most clinically relevant for the individual patient was used. For example in patient with carotid artery disease aortic diameter was evaluated by US, whereas the other methods were used in patients with lower extremity or renal artery disease in whom there was a clinical indication for morphology of the abdominal aorta and its branches. The presented data are therefore based on both US, CT, MRI and angiographic evaluations, with slightly

Table 2 Characteristics of patients with peripheral arterial disease who survived or died during 4.8(0.5) years follow-up. Values are mean (SEM)

Variable	All patients ($n = 511$)	Survivors ($n = 341$)	Non-survivors ($n = 170$)	p Value
Gender male/female		194/147	88/82	0.000
Age (years)	70(12)	67(12)	76(9)	0.000
Body mass index (kg/m^2)	25.9(4.5)	26.2(4.7)	25.0(4.7)	0.132
APC-PCI[a] (μg/L)	0.28(0.19)	0.40(0.45)	0.38(0.76)	0.033
Aortic diameter (mm)	23.8(7.5)	23.6(6.7)	24,3(8.8)	0.923
Systolic blood pressure (mm Hg)	148(24)	150(24)	144(23)	0.029
Diastolic blood pressure (mm Hg)	76(13)	77(13)	72(12)	0.001
B-hemoglobin (g/L)	133(17)	137(17)	125(16)	0.000
B-leukocytes ($\times 10^9$/L)	8.4(3.1)	8.1(2.8)	9.0(3.6)	0.004
P–C-reactive protein (mg/L)	14(31)	11(23)	22(43)	0.000
P-creatinine (μmol/L)	115(108)	104(95)	138(129)	0.000
P-total cholesterol (mmol/L)	4.4(1.06)	4.5(1.05)	4.3(1.06)	0.205
F–P-triglycerides (mmol/L)	1.4(0.9)	1.5(1.0)	1.3(0.6)	0.484
P-high density lipoprotein (mmol/L)	1.3(0.4)	1.3(0.4)	1.3(0.5)	0.877
P-low density lipoprotein (mmol/L)	2.6(1.0)	2.6(1.0)	2.5(1.0)	0.358
F–P-glucose (mmol/L)	6.7(2.7)	6.9(2.9)	6.4(2.3)	0.329

B blood, *P* plasma, *F* fasting

[a] Activated protein C–protein C inhibitor complex

different principles for diameter evaluation. All the different imaging modalities used are well established and regularly validated at our clinic, however.

Furthermore, patients were not systematically assessed for thoracic or iliac aneurysms: Such aneurysms are much more uncommon compared to AAA, however, with prevalences between 0.16 and 0.34 % [36].

Effects of medication might also have affected our results. Warfarin treated patients were excluded as warfarin is known to affect protein C synthesis. However, statins might also be of importance in this context as statin-treated patients with abdominal aortic aneurysm show higher APC-PCI complex levels [37]. Statin treatment is routinely given to all patients hospitalized for peripheral atherosclerosis at our department, however [38], and major differences between groups in this respect are therefore highly unlikely.

Our sample reflects advanced PAD and it might well be that both APC-PCI complex patterns and AAA prevalence might be different among outpatients with stable PAD such as moderate claudication, asymptomatic carotid artery stenosis etc.

Conclusions

APC-PCI complex levels correlated to aortic diameter, and were higher in patients with AAA. A cut-off level of ≥0.15 μg/L, for APC-PCI had high sensitivity but also high negative predictive value, and a low specificity for AAA. APC-PCI complex levels can therefore not be used as a marker for AAA in an arteriosclerotic population, but only to rule out AAA in the few patients below the cut-off level. The potential usefulness of APC-PCI complex levels as a screening marker for AAA in a "healthy" population needs to be further evaluated. The prevalence of AAA was 13 % among patients hospitalized for PAD, highlighting the need for AAA screening within this group.

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Conflict of interest None of the authors have any conflicts of interest to disclose.

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Paper II

The importance of socioeconomic factors for compliance and outcome at screening for abdominal aortic aneurysm in 65-year-old men

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Objective: **To evaluate compliance with screening and prevalence of abdominal aortic aneurysm (AAA) in relation to background data regarding area-based socioeconomic status.**
Methods: **Our department annually invites 4300 65-year-old men from the city of Malmö and 15 neighboring municipalities to ultrasound AAA screening. In a cross-sectional cohort study, compliance and AAA prevalence among 8269 men were related to background socioeconomic data such as mean income, proportion of immigrants, percentage of subjects on welfare, smoking habits, and unemployment rate in the different municipalities. The 10 different administrative areas in Malmö were evaluated separately.**
Results: **Compliance with screening in the entire area was 6630/8269 (80.2%) but varied between 64.4% and 89.3% in different municipalities ($P < .001$). In univariate analysis, compliance increased with increasing mean income ($r = 0.873$; $P < .001$) but decreased with increasing proportion of immigrants ($r = -0.685$; $P = .005$) and subjects on welfare ($r = -0.698$; $P = .004$). Compliance in 10 different administrative parts of Malmö ($P = .002$) also increased with increasing mean income ($r = 0.948$; $P < .001$), and decreased with increasing proportion of immigrants ($r = -0.650$; $P = .042$) and increasing unemployment rate ($r = -0.796$; $P = .006$). Altogether, 117 (1.8%) AAAs were found, the prevalence differing between both different municipalities ($P = .003$) and the 10 different administrative parts of Malmö ($P = .02$). The prevalence of AAA in the 10 administrative parts of Malmö increased with increasing percentage of smokers ($r = 0.784$; $P = .007$), percentage of immigrants ($r = 0.644$; $P = .044$), and unemployment rate ($r = 0.783$; $P = .007$) but decreased with increasing mean income ($r = -0.754$; $P = .012$).**
Conclusions: **Compliance with ultrasound screening for AAA differed between different geographical areas. In areas with low socioeconomic status, compliance rates were lower, whereas AAA prevalence was higher. The identification of contextual factors associated with low compliance is important to be able to allow targeted actions to increase efficacy of ultrasound screening for AAA. Targeted actions to increase compliance in those areas are being scientifically investigated and implemented. (J Vasc Surg 2013;58:50-5.)**

The presence of an abdominal aortic aneurysm (AAA), defined as aortic diameter ≥30 mm, is related to risk for rupture and death. Screening with ultrasound for AAA among 65-year-old men has been proven to reduce AAA-related mortality in a cost-effective way.[1-5] Population-based screening programs have therefore been launched in several countries including Sweden, and since September 2010, all 65-year-old men in the County of Skåne in southwestern Sweden were invited to AAA-screening. Since the remaining longevity of 65-year-old men in Sweden has increased from 14 years to 18 years[6] between 1960 and 2011, it is of great value to find men with AAA to prevent rupture-related mortalities.

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A well-known problem in all population-based screening programs, however, is the varying degree of compliance in different populations, which decreases the medical benefits of the screening procedure.[7] In screening programs for breast cancer, compliance has been shown to be influenced by area-based socioeconomic status (SES), being lower in the parts of the population harboring the highest prevalence of disease.[8,9] This issue is relevant also in the context of AAA-screening, as data from the Multicenter Aneurysm Screening Study have suggested both higher AAA prevalence and lower compliance in subjects living in areas with indices of social deprivation.[10] The importance of different indicators of area-based SES for compliance and aneurysm prevalence at AAA screening therefore need to be investigated in more detail.

SES is a complex multifactorial variable, which has been shown to influence not only adherence to screening programs, but also many other aspects of human health.[11-13] For example, studies have demonstrated relationships between SES and increased risk for a wide range of chronic diseases such as coronary heart disease,[14-16] diabetes mellitus,[17-19] obstructive sleep apnea syndrome,[20] cardiovascular mortality,[21-23] and cancer.[21,24]

One aim of this study was to evaluate compliance with AAA-screening in relation to area-based background

socioeconomic and demographic characteristics of 16 different municipalities in southwestern Sweden and in the 10 different administrative parts of Malmö, the regional capital. Knowledge about potential relationships between screening compliance and SES might help us to identify reasons for noncompliance and to tailor specific measures to improve the compliance in specific community groups.

The other aim was to evaluate potential relationships between area-based background socioeconomic factors and AAA prevalence in the area. Therefore, area-based socioeconomic factors were also related to AAA prevalence in men who did comply with the AAA screening.

METHODS

Between 2010 and 2011, all men born in 1945-1946 (n = 8269) from the city of Malmö and 15 neighboring municipalities in the southwestern part of the County of Skåne were invited to the screening facilities at the Department of Vascular Diseases, Skåne University Hospital, Malmö for AAA screening.

Invitations to the screening were sent to all 65-year-old men in the southwest region of Sweden. With the usage of a population register (www.skatteverket.se), coverage of the area of interest was achieved. Invitations were written in Swedish with referral to an internet address for information on other languages. If subjects did not attend screening after the first invitation, another one was sent. Subjects had the opportunity to reschedule the appointment. The cost for the screening was 130 SEK (19 USD).

Ultrasound investigation of the aorta was carried out with a LOGIQe ultrasound machine and 3.5-12 MHz probes (General Electric Healthcare Inc, Chalfont St. Giles, UK) by biomedical scientists and registered vascular nurses after completion of a special training course in ultrasound examination and a formal examination by a radiologist specialized in ultrasound imaging. In 1.1% of cases where ultrasound was not conclusive (eg, obesity), patients were referred to a conventional computer tomography (CT) scan without contrast, without additional cost for the patient. The maximal infrarenal anteroposterior diameter of the aorta was evaluated, and an AAA was defined as aortic diameter ≥30 mm, using the leading edge to leading edge technique.[25]

We compared the proportion of men who complied with screening in Malmö and its 15 neighboring municipalities (Burlöv, Eslöv, Hörby, Höör, Kävlinge, Landskrona, Lomma, Lund, Malmö, Sjöbo, Skurup, Staffanstorp, Svalöv, Svedala, Trelleborg, and Vellinge). Malmö is the largest municipality in the County of Skåne, hence, it was subdivided into 10 different districts according to the administrative divisions of the city (www.malmo.se). Socioeconomic data was obtained from Statistics Sweden, a federal administrative agency (www.scb.se). Compliance rates were thereafter related to socioeconomic variables registered in each municipality or district, such as mean income, proportion of immigrants, percentage of subjects on welfare, smoking habits, and unemployment rate. Compliance was also evaluated in relation to the distance in kilometers from the screening center to the largest community in each municipality. To map out the different geographical areas, we matched postal codes with the corresponding municipality and the 10 districts of Malmö by a postal code database developed by Postnummerservice (www.postnummerservice.se), a company serving the Swedish postal service. Latest available background socioeconomic data were used, from 2011 for the different municipalities and from 2007 for the 10 districts of Malmö. Background data on daily active smoking was collected from the 2008 public health survey in the County of Skåne (www.skane.se/upload/Webbplatser/folkhalsa/102923_fh-08_INL.pdf).

Mean income was defined as the total yearly income for 20- to 64-year-old subjects, divided by the number of people aged 20-64 at the end of the year. Zero-income earners were included.

Unemployment rate was defined as the percentage of the population between 20 and 64 years of age without employment according to a registry held by the employment service (Arbetsförmedlingen, www.arbetsformedlingen.se).

An immigrant was defined as a subject born outside Sweden. Data on the proportion of subjects on welfare were obtained from The National Board of Health and Welfare (www.socialstyrelsen.se). The classification of higher education was made according to the Swedish Educational Nomenclature (www.scb.se/UFO0506). Higher education was defined as post-secondary school.

Statistics. The Kruskall-Wallis test was used to evaluate differences in continuous variables between groups. Correlations between different variables were tested with Spearman's rank correlation coefficient. Logistic regression analysis was performed including all variables differing between groups. SPSS software v. 20 (SPSS Inc, IBM, New York, NY) was used for the statistical calculations. A P value of $<.05$ was considered significant.

The study was approved by the ethics committee of Lund University.

RESULTS

Compliance. Compliance with screening in the entire area comprising 16 municipalities was 6630/8269 (80.2%). However, figures varied between 64.4% and 89.3% in different municipalities ($P < .001$). The compliance for each municipality is shown in Table I, and compliance in the 10 different districts in Malmö is shown in Table II.

Compliance was related to background variables in the different municipalities (Table III), such as mean income ($r = 0.873$; $P < .001$, Fig 1), percentage of subjects on welfare support ($r = -0.698$; $P = .004$), and proportion of immigrants ($r = -0.685$; $P = .005$). On the other hand, compliance was not related to distance to the screening site ($r = -0.259$; $P = .333$), unemployment rate ($r = -0.247$; $P = .375$), proportion of subjects with higher education ($r = 0.496$; $P = .060$), or smoking rates ($r = -0.132$; $P = .625$).

Table I. Compliance with screening for AAA and the prevalence of screening-detected AAAs in the city of Malmö and 15 neighboring municipalities

Municipality	*Invited, No.*	*Screened, No.*	*Compliance, %*	*AAA, %*
Burlöv	193	151	78.2	2.0
Eslöv	319	257	80.6	1.5
Hörby	163	126	77.3	3.1
Höör	256	214	83.6	2.3
Kävlinge	392	334	85.2	2.1
Landskrona	542	385	71.0	1.3
Lomma	276	246	89.1	2.4
Lund	1136	902	79.4	1.2
Malmö	2664	2077	78.0	1.7
Sjöbo	303	248	81.8	2.8
Skurup	207	170	82.1	1.8
Staffanstorp	269	237	88.1	2.1
Svalöv	195	140	71.8	2.8
Svedala	244	218	89.3	1.8
Trelleborg	578	462	79.9	1.7
Vellinge	507	449	88.6	1.1

AAA, Abdominal aortic aneurysm.

Table III. Relationships of socioeconomic factors with compliance with screening for AAA and with the prevalence of screening-detected AAAs in the city of Malmö and 15 neighboring municipalities

	Compliance, %		*AAA prevalence, %*	
Variables	r	P *value*	r	P *value*
Mean income	0.873	<.001	−0.118	.676
Proportion with higher education	0.496	.060	0.387	.154
Proportion of immigrants	−0.685	.005	−0.347	.206
Percentage of unemployment	−0.247	.375	0.192	.492
Percentage of subjects on welfare support	−0.698	.004	0.065	.817
Distance to screening site	−0.259	.333	–	–
Smoking rate among 18-80 year old men	−0.132	.625	−0.204	.450

AAA, Abdominal aortic aneurysm.

In the city of Malmö, compliance differed between the 10 administrative parts ($P = .002$) and was related to background variables in the different districts (Table IV) such as mean income ($r = 0.948$; $P < .001$; Fig 2), unemployment rate ($r = -0.796$; $P = .006$; Fig 3), distance to the screening site ($r = 760$; $P = .011$) and proportion of immigrants ($r = -.650$; $P = .042$). On the other hand, compliance was not related to smoking ($r = -0.565$; $P = .089$), percentage of subjects on welfare support ($r = -0.431$; $P = .214$), or the proportion of subjects with higher education ($r = 0.015$; $P = .967$).

When compliance was related to all different socioeconomic variables in multivariate analyses, the significant correlations found with different individual socioeconomic variables disappeared.

Table II. Compliance with screening for AAA and the prevalence of screening-detected AAAs in 10 different administrative areas in the city of Malmö

Administrative area	*Invited, No.*	*Screened, No.*	*Compliance, %*	*AAA, %*
Centrum	405	301	74.3	1.0
Fosie	331	246	74.3	2.4
Husie	178	145	81.5	1.4
Hyllie	364	291	79.9	1.7
Kirseberg	125	98	78.4	2.0
Limhamn/Bunkeflo	475	410	86.3	0.7
Oxie	133	117	88.0	1.7
Rosengård	165	116	70.3	2.6
Södra innerstaden	191	123	64.4	4.1
Västra innerstaden	297	230	77.4	2.1

AAA, Abdominal aortic aneurysm.

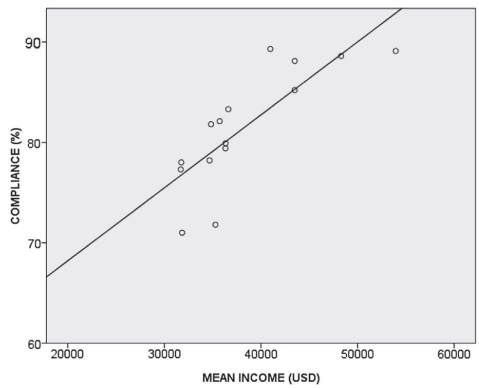

Fig 1. Relationship between compliance with abdominal aortic aneurysm (AAA) screening and mean yearly income in 16 municipals in the County of Skåne ($r = 0.873$; $P < .001$).

AAA prevalence. A total of 117 AAAs (1.76%) were detected. The number of AAAs in the different municipalities are shown in Table I, and the number of AAAs in the 10 different districts in Malmö in Table II. AAA prevalence differed between the 16 municipalities ($P = .003$).

The prevalence of screening detected AAAs was not significantly related to background variables in the different municipalities such as mean income ($r = -0.118$; $P = .676$), percentage of subjects with higher education ($r = -0.387$; $P = .154$), proportion of immigrants ($r = -0.347$; $P = .206$), unemployment rate ($r = 0.192$; $P = .492$), proportion of subjects on welfare support ($r = 0.065$; $P = .817$), or the smoking rate ($r = -0.204$; $P = .450$).

In the city of Malmö, the prevalence of screening detected AAAs differed between the 10 administrative parts ($P = .020$) and was significantly related to background variables in the different districts such as smoking rate ($r = 0.784$; $P = .007$), unemployment rate ($r = 0.783$;

Table IV. Socioeconomic relationships between compliance with screening for AAA and the prevalence of screening-detected AAAs in 10 different administrative areas in Malmö

	Compliance, %		*AAA prevalence, %*	
Variables	r	P *value*	r	P *value*
Mean income	0.948	<.001	−0.754	.012
Proportion with higher education	0.015	.967	−0.404	.247
Proportion of immigrants	−0.650	.042	0.644	.044
Percentage of unemployment	−0.796	.006	0.783	.007
Percentage of subjects on welfare support	−0.431	.214	0.462	.179
Smoking rate among 18- to 80-year-old men	−0.565	.089	0.784	.007

AAA, Abdominal aortic aneurysm.

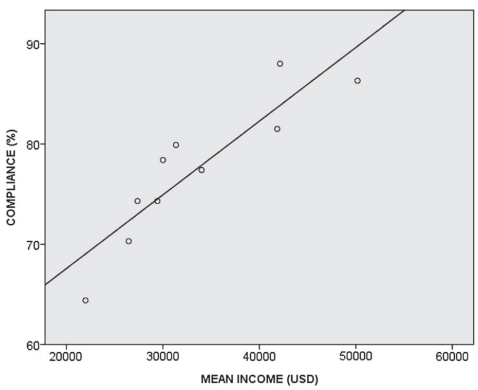

Fig 2. Relationship between compliance with abdominal aortic aneurysm (AAA) screening and mean yearly income in 10 different administrative areas in Malmö ($r = 0.948$; $P < .001$).

$P = .007$), mean income ($r = -0.754$; $P = .012$) and proportion of immigrants ($r = 0.644$; $P = .044$), but not to the percentages of subjects with higher education ($r = -0.404$; $P = .247$) or welfare support ($r = 0.462$; $P = .179$).

When AAA prevalence was related to all different socioeconomic variables in multivariate analyses, the significant correlations found with different individual socioeconomic variables disappeared.

DISCUSSION

We found large differences in compliance with AAA screening, both between different municipalities, and between different parts of Malmö. As previously indicated when evaluating compliance in relation to a composite score reflecting social deprivation,[10] we also found evident

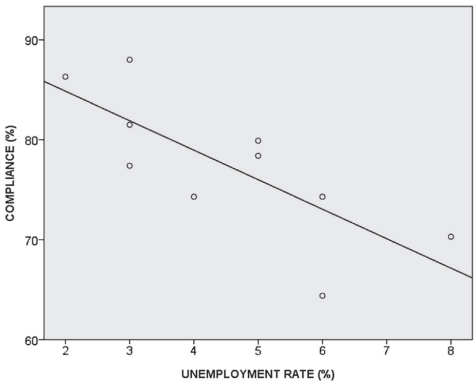

Fig 3. Relationship between compliance with abdominal aortic aneurysm (AAA) screening and unemployment rate in 10 different administrative areas in Malmö ($r = -0.954$; $P < .001$).

univariate correlations between several different variables reflecting background area-based SES at the area level with both AAA prevalence and screening compliance. The willingness of 65-year-old men to comply with an invitation to AAA screening was related to mean income and the proportion of immigrants in the area where they reside, both when comparing different municipalities and different parts of Malmö. Furthermore, we found relationships with percentage on welfare support when comparing municipalities and with unemployment rate when comparing different parts of Malmö. We have no good explanation for the somewhat differing results in these two comparisons.

Factors reflecting area-based SES might be related to the degree of trust in other people, authorities and organizations, as well as with participation in social factors that might in turn affect participation in screening programs. A plausible explanation for the relationships between compliance and the proportion of immigrants could be that this group is integrated in the Swedish society to a limited extent because of language barriers.

Several previous reports, including publications from the Malmö population, have shown relationships between SES and increased morbidity.[16] When evaluating the above results, several limitations of our study approach should be considered. Relationships between compliance and AAA-prevalence on one hand and the different socioeconomic variables on the other could not be reproduced in multivariate analysis. This is probably due to the fact that socioeconomic variables such as education, unemployment, income, and proportion on welfare are highly correlated to each other. Furthermore, we studied compliance in a sex- and age-specific group, 65-year-old men, and related this figure to data from the entire background population of the corresponding geographical area. Area- based SES among 65-year-old men may not necessarily be the same as

in a sex-mixed total population; one might only postulate such a relationship. Area-based SES might also differ between compliant and noncompliant men. To properly address this issue, however, we would have needed access to full individual SES data not only for all individuals screened, but also for noncompliant subjects. The fact that we do not have access to these data and, therefore, have analyzed background area-based SES constitutes the major limitation of the study design.

Data on smoking were not solely derived from 65-year-old men in the different municipals, but instead from men between 18 and 80 years of age in 2008 (ie, 2-3 years before screening). As smoking nowadays is less common in the younger generation, and young Swedish people more frequently use moist snuff compared with cigarettes, these figures may not accurately reflect smoking habits among 65-year-old Swedish men, among whom the proportion of daily smokers has declined from 32% in 1980 to 11% in 2007.[26] Even though the role of smoking for the development of AAA is well established,[26] area smoking rates in our report should only be regarded as markers of lower SES.

As we found no evident relationships between the distance from the respective municipality or district and compliance to AAA screening, our findings did not support the idea of ambulant AAA screening that is used in some districts in Sweden. However, it has to be remembered that our area is, at least by Swedish standards, densely populated with short distances between different hospital facilities and a well-developed public transport system. An ambulant screening approach might well be of great value in more sparsely populated areas, such as reported from Australia.[27] Nevertheless, area-based SES seems to be of greater relevance for the decision to comply or not with AAA screening than the distance to the screening site.

By targeting a number of areas with low compliance and high AAA-prevalence, we aim to increase the compliance in those areas compared with control areas. Screening compliance and disease prevalence are important to evaluate in relation to each other. Both these variables have been evaluated in other screening programs such as for mammography and cervical cancer.[27,28] Zackrisson et al[9] found that compliance to attend mammography was lower among immigrants and those with lower SES. The prevalence of breast cancer was also higher in the same groups.

Prevalence of AAA in our area was 1.8%; this figure is substantially lower than in the studies upon which the decision to start screening with ultrasound for AAA among 65-year-old men was based.[1-5] However, several more recent studies both in our[26] and other countries[29] have confirmed that AAA prevalence among men is decreasing, and our prevalence is well within the recently presented confidence interval for AAA prevalence in central Sweden.[26] This low incidence of AAA made it impossible for us to establish significant differences in AAA incidence between different municipalities in the area or different districts in Malmö. Nevertheless, AAA prevalence was related to several of the same socioeconomic factors in the background population that were of importance for compliance rates. AAAs are more prevalent in 65-year-old men residing in an environment where the background population has low mean income, low educational level, and is composed of a high proportion of immigrants. In this context, a major confounder has to be addressed since smoking is a well-known and accepted risk factor both for AAA development and expansion.[30] It was, therefore, not surprising to notice that in our study, smoking rates correlated significantly with the prevalence of AAA in the districts of Malmö.

Overall, the attendance to our screening was acceptable (80.2%) compared with some mammography screening programs (14%-22%).[31-33] One explanation could be that no private clinics offer AAA screening in Sweden, hence, subjects are not lost to other centers, which seems to be a problem in mammography and cervical cancer screening[27] Whether the efficacy of AAA screening can be increased by screening at a higher age or re-screening of subjects with aortic diameter of 25-30 mm as suggested[26,34] remains to be proven scientifically.

The socioeconomic impact on the efficacy of screening may be greater than the data immediately suggest. The AAA prevalence ranged between 1% and 4% in different areas among individuals who did attend the screening. Area-based SES was related not only to nonattendance, but also to disease prevalence in both this and other studies[10,28] and the AAA prevalence in the nonattending group might therefore be higher.[10] A modest increase of prevalence of 20% in the nonattending group might render the proportion of AAAs that the screening fails to identify as high as 40% in certain areas (Table V, example A). Assuming a double prevalence of AAA in the nonattending group (Table V, example B), more than 50 % of the existing AAAs will be missed by screening.

Table V. Theoretical model showing how an assumed increase of AAA prevalence in the nonattending group might result in a high proportion of missed AAAs

	Area A	*Area B*
Compliance	64%	89%
Prevalence of identified AAAs/1000 inhabitants	4%	1%
Example A		
Prevalence if 20% higher in noncompliant group	5%	1.25%
Number of AAAs in noncompliant group/1000 inhabitants	18	1
Proportion of AAAs missed by screening	41% (18/44)	10% (1/10)
Example B		
Prevalence if double in noncompliant group	8%	2%
Number of AAAs in noncompliant group	29	2
Proportion of AAAs missed by screening	53% (18/44)	18% (1/10)

AAA, Abdominal aortic aneurysm.

CONCLUSIONS

Compliance with ultrasound screening for AAA differed between different geographical areas, and men from areas with low socioeconomic status generally showed lower compliance. The identification of contextual factors associated with low compliance is important to be able to allow targeted actions to increase efficacy of ultrasound screening for AAA. Such action to increase compliance in those areas is now being scientifically investigated and implemented.

AUTHOR CONTRIBUTIONS

Conception and design: JH, MM, BL, AG
Analysis and interpretation: MZ, JH, BL, AG
Data collection: MZ, MR
Writing the article: MZ, JH, AG
Critical revision of the article: MZ, JH, MM, CW-H, MR, AG
Final approval of the article: MZ, JH, BL, AG
Statistical analysis: MZ, AG
Obtained funding: JH, BL, AG
Overall responsibility: MZ, JH, AG

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Paper III

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Short Communication

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Academic vascular unit collaboration with advertising agency yields higher compliance in screening for abdominal aortic aneurysm

Moncef Zarrouk, Anders Gottsäter, Martin Malina and Jan Holst

Abstract

To improve compliance with abdominal aortic aneurysm (AAA) screening in low compliance areas, individually tailored invitations were developed in collaboration with a professional advertising agency. Compliance increased in two intervention municipalities from 71.4% in 2010–2012 to 78.1% in 2013 ($p = 0.025$), and was then higher [odds ratio 1.7; 95% confidence interval 1.1–2.6; $p = 0.013$] than in two control municipalities in which compliance was unchanged (417/552 [75.5%] in 2010–12 and 122/180 [67.8%] in 2013). Compliance with AAA-screening can be increased by collaboration with a professional advertising agency, albeit at a comparably high cost.

Keywords

abdominal aortic aneurysm, screening, advertising agency

Date received: 9 June 2014; accepted: 29 July 2014

Introduction

Ultrasound screening for abdominal aortic aneurysm (AAA, aortic diameter $\geqslant 30$ mm) among 65-year old men reduces AAA-related mortality cost-effectively.[1–6] All 65-year old men in the County of Skåne in Sweden are invited to AAA-screening, however, varying compliance rates decrease screening benefits.[7] We previously identified municipalities with low compliance and high prevalence of AAA as being characterized by low socioeconomic status (SES).[8] We here evaluate the utility of individually tailored screening invitations, developed in collaboration with a professional advertising agency, to improve compliance in such areas.

Methods

The four municipalities with the lowest screening compliance in 2010–11 were Landskrona (71.0%), Svalöv (71.8%), Hörby (77.3%), and Burlöv (78.2%).[8] We chose Landskrona and Hörby as intervention municipalities, and Svalöv and Burlöv as control areas.

In collaboration with an advertising agency (The Fan Club®, Malmö and Stockholm, Sweden), we developed a tailor made screening invitation that included information about AAA and the screening procedure, the date and time for the appointment, and an individual detailed map of the route from each subject's home to our screening facilities. The invitation also included a red tie with a knot tied like an aneurysm with a tag saying "Congratulations, this year is your 65th birthday, and this is a gift from Skåne University Hospital". The cost of the intervention was 15850 €. All invitations were in Swedish but contained a referral in English to a webpage for information in English, Spanish, Dari, Turkish, Persian, Somali, Arabic, Polish, Finnish, and Serbo-Croatian.

During 2013, all men born in 1948 from Landskrona ($n = 190$) and Hörby ($n = 102$) received the above invitation to AAA screening. Men born in 1948 from the control municipalities Burlöv ($n = 101$) and Svalöv ($n = 79$) received standard invitations from the public health system.

Chi Square test was used to evaluate differences between groups. Correlations between variables were tested with Spearman's rank correlation coefficient. SPSS® (SPSS inc, IBM, New York, USA) version 20 was used for statistical calculations. P-values <0.05 were considered significant.

The study was approved by the ethics committee of Lund University.

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Table 1. Compliance with AAA screening before (2010–2012) and after intervention (2013) in control and intervention municipalities (n attending / n invited [%]).

	Before intervention (2010–2012)	After intervention (2013)	p (intervention vs control)
Intervention municipalities	678/949 (71%)	228/292 (78%)	0.013
Control municipalities	417/552 (76%)	122/180 (68%)	

Results

Overall screening compliance in the four municipalities in 2010–12 before intervention was 72.9%. Compliance in the two intervention municipalities increased from 71.4% in 2010–12 to 78.1% in 2013, significantly higher (odds ratio = 1.7; 95% confidence interval 1.1–2.6; p = 0.013) than in the two control municipalities, where it remained unchanged (75.5% in 2010–12 and 67.8% in 2013) (see Table 1).

Discussion

Because low compliance decreases the cost-effectiveness of screening programmes, different methods have been evaluated to address the problem, for example in breast and colorectal cancer screening[9,10], and tailored invitations (though not designed or developed by professional advertising agents), telephone counselling, reminder letters, and combinations of these methods have been shown to significantly increase compliance.[9,10] Ours is the first study documenting that tailored invitations developed in collaboration with a professional advertising agency were more efficient than standard invitations in increasing previously low AAA-screening compliance rates in areas with low SES.

The text of the tailored invitation was more explicit and comprehensive compared with the standard invitation, and the individualized travel-map for each subject might also have helped them to locate screening facilities up to 60 kilometers from their homes. The gift tie might have illustrated the mechanics of an AAA, and may also have persuaded men in the intervention group that the health care system had a genuine interest in their health.

The advertising agency cost was 15850 € (83 €/subject). If compliance in the intervention municipalities (71.4 % in 2010–2012) had been unchanged in 2013, 208 men would have been expected to attend screening – 20 fewer men than actually attended in 2013 (228/292). The intervention cost per additional subject attending screening in the intervention municipalities was thus 793 €. Assuming an AAA prevalence of 1.76 % (as previously demonstrated[8]), the cost per additionally detected AAA was 45057 € (793 € / 0.0176). In our previous analysis,[8] prevalence in the municipalities we subsequently chose for intervention was higher than in the whole area: 2.6% corresponding to a hypothetical cost of 30500 € (793 € / 0.026) per AAA detected.

The mean total cost for AAA surgery in our institution is 33277 € (range 1243-329714 €) in elective cases, and 44593 € (range 1473-323661 €) in emergency ruptured cases. Elective repair of a screen-detected AAA instead of acute surgery of a ruptured one thus saves 11316 €. Converting 1.4 (15850 € / 11316 €) emergency surgeries to elective surgeries would therefore cover the total cost for our intervention.

Conclusions

Compliance with AAA-screening can be increased by invitations developed in collaboration with a professional advertising agency, albeit at a comparably high cost. Screening programmes should evaluate reasons for non-attendance and consider tailored measures to increase compliance and cost-benefits.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Paper IV