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# Abdominal Aortic Aneurysm

## *Epidemiological and Health Economic Aspects*

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**Abstract**
Mani, K. 2010. Abdominal Aortic Aneurysm. Epidemiological and Health Economic Aspects. Acta Universitatis Upsaliensis. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 503. 86 pp. Uppsala. ISBN 978-91-554-7670-0.

Abdominal aortic aneurysm (AAA) is a common disease that is life threatening when rupture occurs. The aims of this thesis were to study (I) the long-term survival after AAA repair, (II) the cost of repair with open (OR) and endovascular (EVAR) technique, (III) the effect of different statistical methods on interpretation of cost data, (IV) the prevalence of the disease among patients with suspected arterial disease referred to the vascular laboratory, and (V) the cost-effectiveness of selective high-risk screening. Analyses of data from the Swedish vascular registry (Swedvasc), local patient registries, patient records and hospital cost registries form the basis of this thesis.

Short- and long-term survival after intact AAA repair improved over the past two decades, despite increasing patient age and rate of comorbidities over time. Compared to a general population adjusted for age, sex and calendar year, the relative 5-year survival was 90% among those surviving repair. While short-term survival improved over time after ruptured repair, relative long-term survival was stable. Despite differences in patient selection and cost structure, the total cost of AAA repair with EVAR and OR was similar in a population based setting (€28,193). There was lack of consistency in the methods used in cost-analysis in the current literature, and p-values were highly dependent on test method.

The practice of selective (non-population-based) screening for AAA among patients referred to the vascular laboratory was studied. The prevalence of AAA was 4.2% among male and 1.5% among female patients. AAA was associated with high age and prevalence of arterial stenosis. Of AAAs detected through selective screening, 21.5% had undergone elective repair at 7.5 years follow-up. In a health-economic evaluation, the incremental cost-effectiveness ratio of selective screening was €11,084 per life year gained.

In conclusion, survival after intact AAA repair has improved over time, despite changes in case-mix. Results of health economic reports on cost of AAA repair can be highly dependent on patient selection as well as presentation of data and the statistical methods used. Selective screening for AAA among patients referred to the vascular laboratory is cost-effective.

*Keywords:* Abdominal aortic aneurysm, cost, cost-effectiveness, endovascular aneurysm repair, screening, surgery, survival

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*Science is nothing but developed perception,*
*interpreted intent, common sense rounded out*
*and minutely articulated.*
*George Santayana (1863-1952)*

# List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Mani K, Björck M, Lundkvist J, Wanhainen A. Improved long-term survival after abdominal aortic aneurysm repair. Circulation 2009; 120(3): 201-211.

II Mani K, Björck M, Lundkvist J, Wanhainen A. Similar cost for elective open and endovascular AAA repair in a population-based setting, J Endovasc Ther 2008; 15:1-11.

III Mani K, Lundkvist J, Holmberg L, Wanhainen A. Challenges in analysis and interpretation of cost data in vascular surgery. J Vasc Surg 2009*; in press.*

IV Ålund M, Mani K, Wanhainen A. Selective screening for abdominal aortic aneurysm among patients referred to the vascular laboratory. Eur J Vasc Endovasc Surg 2008; 35(6): 669-674.

V Mani K, Ålund M, Björck M, Lundkvist J, Wanhainen A. Screening for abdominal aortic aneurysm among patients referred to the vascular laboratory is cost-effective. Eur J Vasc Endovasc Surg 2009; *in press.*

*Cover picture:*
Wooden sculpture of an infrarenal abdominal aortic aneurysm, by the multi-talented artist Anders Wanhainen. Photography kindly provided by Matti Rantatalo.

# Contents

# Abbreviations

| | |
|---|---|
| AAA | Abdominal aortic aneurysm |
| CI | Confidence interval |
| EVAR | Endovascular aneurysm repair |
| iAAA | Intact abdominal aortic aneurysm |
| ICER | Incremental cost-effectiveness ratio |
| ICU | Intensive care unit |
| ISCVS | International Society for Cardiovascular Surgery |
| LYG | Life years gained |
| NICE | National Institute for Health and Clinical Excellence |
| NPR | National population registry |
| OR | Open repair |
| PIN | Personal identification number |
| QALY | Quality adjusted life years |
| rAAA | Ruptured abdominal aortic aneurysm |
| SD | Standard deviation |
| SMR | Standardized mortality ratio |
| SVS | Society for Vascular Surgery |
| Swedvasc | The Swedish Vascular Registry |

# Introduction

The term aneurysm originates from the Greek word Ανεύρισμα (Aneurysma), meaning a widening. An aneurysm in medical terminology is equal to a permanent localized dilatation of a blood vessel. An abdominal aortic aneurysm (AAA) is thus a dilatation of the abdominal aorta, Figure 1. The dilatation is related to a weakening of the aortic wall, which most often occurs in the abdominal aorta below the renal arteries, and is referred to as an infrarenal AAA. The natural course of an AAA is to gradually expand with an increasing risk of rupture, which represents an immediate emergency with high mortality. Treatment of AAA is achieved through an operation where the dilated aorta is replaced with a synthetic graft. This can either be performed with open surgery (open repair, OR) or an endovascular operation (endovascular aneurysm repair, EVAR). If the AAA is detected prior to rupture, operative treatment is preferably performed as a preventive measure (intact AAA repair, iAAA). However, operation can also be performed as an emergency treatment after rupture (ruptured AAA repair, rAAA).

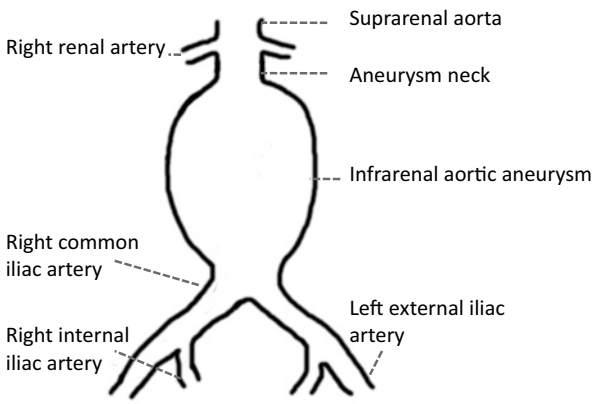


Figure 1. Schematic drawing of an infrarenal abdominal aortic aneurysm.

# Historical perspectives

The Belgian anatomist and physician Vesalius (1514-1564) was one of the first to describe an AAA (Fortner, 1984). The treatment of aneurismal disease consisted primarily of ligation during the 18th and 19th century. Several innovative techniques such as external compression, wiring and electrocoagulation and cellophane wrapping were tried in the late 19th and first half of the 20th century (Fortner, 1984). The first successful reconstructive AAA repair was performed in 1951 by Freeman and Leeds (Freeman, 1951) and in the following years, the first repair of a rAAA was performed (Bahnson, 1953). Early on, freeze-dried homograft was used to replace the aorta (Dubost, 1952), which subsequently was replaced by more durable synthetic prostheses such as Vinyon-N cloth (Voorhees, 1952) and knitted Dacron (De Bakey, 1958). The innovative technique of endovascular aneurysm repair was first described by Volodos in the Russian medical literature (Volodos, 1986), and was later disseminated in clinical practice by Parodi (Parodi, 1991).

# Definition

There are several parallel definitions of AAA (McGregor, 1975; Sterpetti, 1987; Collin, 1988; Johnston, 1991). According to the ISCVS/SVS Ad Hoc Committee, an AAA is defined as an infrarenal aortic diameter 1.5 times larger than the expected (Johnston, 1991). This definition takes into account the interpersonal variation in aortic diameter due to differences in gender, age and body surface area (Pearce, 1993; Sonesson, 1994; Grimshaw, 1997). However, the definition most often used in clinical practice is to regard an infrarenal abdominal aorta of 30 mm or more as an AAA (McGregor, 1975). The basis for this definition is an angiographic study of the normal distribution of abdominal aortic diameter in the population, and the fact that an infrarenal aortic diameter of 30 mm is well above the average diameter for both sexes (Steinberg, 1965). Thirty millimeters as the upper limit for normal aortic diameter was confirmed in a recent population-based magnetic resonance tomography study of aortic size (Wanhainen, 2008).

# Epidemiology

## Prevalence of AAA

Prevalence of AAA has been studied based on two modalities: autopsy series (McFarlane, 1991; Bengtsson, 1992) and ultrasonographic screening programs (Collin, 1988; Scott, 1995; Lindholt, 1997; Lederle, 2000; Ashton,

2002). According to a comprehensive autopsy study with an autopsy rate of 85% from the city of Malmö in Sweden (Bengtsson, 1992), the overall prevalence of AAA was 4.3% in men and 2.1% in women and was age dependent, Figure 2.

In an ultrasonographic screening study of more than 126,000 veterans in the United States between the age of 50 and 79 years the prevalence of AAAs ≥3cm was 4.2% and ≥4cm 1.3% (Lederle, 2000). The highest prevalence of AAA in a general population was found in the Norsjö municipality in Northern Sweden, with an AAA prevalence of 16.9% among men 65-75 years old (Wanhainen, 2001).

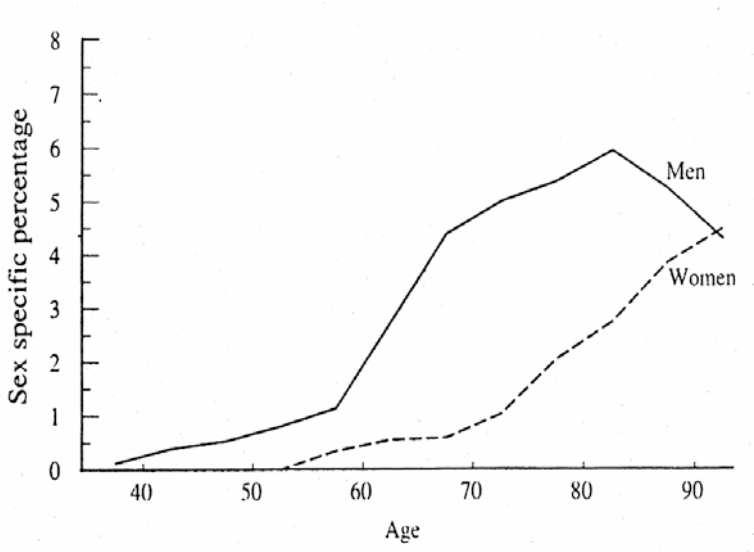


Figure 2. Prevalence of AAA among men and women at different ages. Reprint from Bengtsson, 1992, with permission of the authors.

The prevalence of AAA is related to the prevalence of risk factors for AAA in the society and some studies indicate that the prevalence of AAA is increasing in Western countries (Bengtsson, 1992; Acosta, 2006). Smoking is the most important risk factor for AAA (Lederle, 2000). Other factors associated with the disease include high age, male gender, positive family history and white race while diabetes is negatively associated with the prevalence of AAA (Lederle, 2000).

Atherosclerotic disease is associated with AAA as an independent risk factor (Lederle, 2000), and the prevalence of AAA is high in patients with occlusive arterial disease (Bengtsson, 1988; Bengtsson, 1989). However, studies show divergent results regarding association of AAA with hypercholesterolemia and hypertension that are components of atherosclerosis devel-

opment (Strachan, 1991; Krohn, 1992; Louwrens, 1993; Pleumeekers, 1995; Simoni, 1995; Lee, 1997; Naydeck, 1999; Blanchard, 2000; Jamrozik, 2000; Lederle, 2000; Vardulaki, 2000; Newman, 2001; Singh, 2001; Tornwall, 2001; Rodin, 2003).

## Natural course

The natural course of an AAA is to gradually expand and to eventually rupture. However, many patients with AAA are old and have other comorbidities and thus die of other causes than the AAA. In these cases the AAA remains asymptomatic throughout life. Based on an extrapolation of data from the Multicentre Aneurysm Screening Study (Thompson, 2009), it can be estimated that approximately every fourth AAA eventually will rupture. Expansion rate of AAA has been studied in patients unfit for surgery and in studies of small AAAs (Cronenwett, 1990; Limet, 1991; Chang, 1997; 1998; Lederle, 2002; Schlosser, 2008). There is great individual variation in the expansion rate of aneurysms. Overall, AAAs expand exponentially, with increasing expansion rate as the diameter increases. The mean expansion rate of small aneurysms has been reported at 2.5 to 5mm per year (Chang, 1997; Schlosser, 2008). Factors other than aneurysm diameter that have been associated with a higher expansion rate include female gender, smoking and hypertension (Cronenwett, 1990; Chang, 1997; Solberg, 2005; Mofidi, 2007; Schlosser, 2008). To date, there is no established medical intervention that reduces the expansion rate of AAAs (Baxter, 2008). There are, however, indications that statin treatment might be associated with a lower expansion rate (Schlosser, 2008). As smoking is associated with an increased growth rate, smoke cessation is the only available method to reduce the growth rate of a small AAA (MacSweeney, 1994).

The risk of AAA rupture is associated with aneurysm size. Aneurysms with a diameter below 50 mm have a very low rupture rate, while aneurysms between 50 and 60 mm have a 5 to 10% risk of rupture per year (Scott, 1998; The UK Small Aneurysm Trial Participants, 1998; Vardulaki, 1998; Lederle, 2002; Lederle, 2002). The yearly risk of rupture increases significantly above 60 mm and is more than 30% for aneurysms above 70 mm in diameter (Lederle, 2002). Female sex, smoking, hypertension and chronic obstructive pulmonary disease are also associated with an increased risk of rupture (Cronenwett, 1985; Brown, 1999; The UK Small Aneurysm Trial Participants, 2002; Fillinger, 2007).

Even if death in aneurysm rupture is avoided through preventive operation of an iAAA or successful treatment of a rAAA, patients with AAA have associated comorbidities that result in a lower long-term survival than the general population (Johnston, 1994; Aune, 1995; Norman, 1998; Batt, 1999; Hultgren, 2007). Cardiovascular diseases are the main causes of late death in this patient group (Johnston, 1994). Long-term survival among patients with

untreated AAA has only been studied in patients who for various reasons are not surgical candidates. In this group, 5-year survival is as low as 15-40% (Perko, 1993; Englund, 1997).

### Incidence of rupture

Studies of rupture incidence are either retrospective, i.e. based on routine mortality statistics and autopsy reports (Bengtsson, 1993; Choksy, 1999; Heikkinen, 2002; Acosta, 2006), or prospective studies of small aneurysms (Scott, 1998; Ashton, 2002; Lederle, 2002; The UK Small Aneurysm Trial Participants, 2002). Uncertainty in cause of death in cases where autopsy is not performed affects validity of the analyses (Bengtsson, 1993). The reported rupture incidence varies between 1 and 21/100,000 person years (Wilmink, 1998). In an analysis of the Malmö cohort (Bengtsson, 1993), the rupture incidence was 5.6/100,000 individuals (8.4/100,000 men and 3.0/100,000 women). The age-specific incidence was highest in men 81 to 90 years old (113/100,000) and in women older than 90 (68/100,000). The overall mortality rate was 88%. In another population-based study from the UK (Choksy, 1999), three quarters of the patients with a rAAA did not reach the operation theatre, and only 48% of those operated on survived. According to the same report, 12.6% of all rAAAs occurred in men below the age of 65. Fourteen percent of rAAA repairs registered in the Swedish Vascular Registry (Swedvasc) 1994-2005 were among men <65 years old, and 14% were among women (Wanhainen, 2008). In a prospective study among patients with AAAs of 40-55 mm, risk of rupture was four times higher among women than among men (The UK Small Aneurysm Trial Participants, 2002).

Mean aneurysm size at rupture has been reported to be 7 to 8 cm (Choksy, 1999; Heikkinen, 2002). While most ruptures occur in large AAAs, small aneurysms may also rupture. In a Finnish study (Heikkinen, 2002) 5% of all rAAAs in men and 24% in women were below 5.5 cm in diameter.

Some contemporary reports indicate that the incidence of AAA rupture is increasing (Heikkinen, 2002; Acosta, 2006). According to Heikkinen et al, the annual number of rAAAs may increase 50% over the coming two decades. However, studies from the United States indicate a decrease in incidence of rAAA repairs over the past decades (Dillavou, 2006; Mureebe, 2008), and the incidence of rAAA repairs was stable in Sweden 1994-2005 (Wanhainen, 2008).

## Operative treatment

Surgical repair of AAAs can be classified according to symptoms prior to surgery in five groups: 1) elective asymptomatic, 2) elective symptomatic, 3)

emergent repair without rupture, 4) rupture without clinical shock and 5) rupture with clinical shock (Eriksson, 1979). Perioperative mortality is lowest in group 1 and highest in group 5. In practice, AAA repairs are often divided into elective AAA repair (groups 1 and 2) and emergent AAA repair (groups 3-5), or into iAAA repair (groups 1-3) and rAAA repair (groups 4 and 5).

## Intact AAA repair

The adequate AAA size at which elective repair is recommended in asymptomatic patients has been established to 55 mm in two large, randomized multi-centre studies (The UK Small Aneurysm Trial Participants, 1998; Lederle, 2002; Powell, 2007). However, an individual approach is recommended, where the operative risk of the patient is balanced against risk of rupture and expected long-term survival. Elective operative treatment is associated with a perioperative mortality of 2-5% in large randomized or population-based studies (The UK Small Aneurysm Trial Participants, 1998; Lederle, 2002; Greenhalgh, 2004; Prinssen, 2004; Wanhainen, 2008). National variations in perioperative mortality after AAA repair exist in register data (Gibbons C, 2008). Short-term outcome is highly dependent on patient comorbidities, and mortality is increased in patients with renal dysfunction, cardiac disease and pulmonary dysfunction (Steyerberg, 1995). In addition, increased age and female gender are associated with higher short-term mortality (Wanhainen, 2008). Most but not all (Heller, 2000) reports indicate a reduced operative mortality after iAAA repair over time (Wainess, 2004; Cowan, 2006; Dillavou, 2006; Wanhainen, 2008). A minority of iAAA repairs are performed in symptomatic patients e.g. with tender aneurysms. In these cases operation is performed as an urgent intervention, and the perioperative mortality is approximately twice as high as in elective asymptomatic repair (Gibbons C, 2007; Wanhainen, 2008).

Based on the Swedvasc, time-trends for AAA repair in Sweden between 1994 and 2005 were recently reported (Wanhainen, 2008). During this period, the incidence as well as the total crude number of operations performed for iAAA increased significantly. This was mainly due to the introduction of EVAR, as discussed below. In addition, patient demography changed over time with an increase in mean age of AAA patients and a higher proportion of octogenarians being treated. The 30-day mortality rate decreased steadily over the studied time-period, both after iAAA and rAAA repair. Changes in patient demography could, however, affect long-term survival after AAA repair, potentially reducing the expected benefit for the patients. Long-term survival is fundamental for surgical decision-making, and has important health economic implications when evaluating the cost-effectiveness of a new treatment (e.g. EVAR) or health intervention (e.g. screening for AAA).

As discussed previously, there are two different methods for treatment of AAA: OR and EVAR. There are advantages and disadvantages with both techniques. OR is associated with a higher perioperative mortality and morbidity, as well as longer ICU and hospital stay than EVAR (Greenhalgh, 2004; Prinssen, 2004; Lederle, 2009). While EVAR has several advantages in lower perioperative mortality and morbidity, this treatment is associated with a higher rate of re-interventions and need for close follow-up (Prinssen, 2004). Due to the novelty of the method and the rapid development of the endovascular technique, long-term durability of EVAR is not as well known as after OR. In addition, EVAR is associated with certain requirements in aneurysm morphology, most importantly a need of an aneurysm neck as a proximal sealing zone for the endovascular stentgraft. Approximately 30-50% of all AAAs are currently regarded as not possible to treat with EVAR (although this varies considerably between centers), and future development of the technique might decrease this proportion (Garcia-Madrid, 2004; Greenhalgh, 2004; Prinssen, 2004). Current practice at many centers is to select patients to OR or EVAR based on aneurysm morphology as well as patient age and comorbidities. Patients treated with EVAR are typically older and have more comorbidities than those treated with OR (Garcia-Madrid, 2004; Wanhainen, 2008).

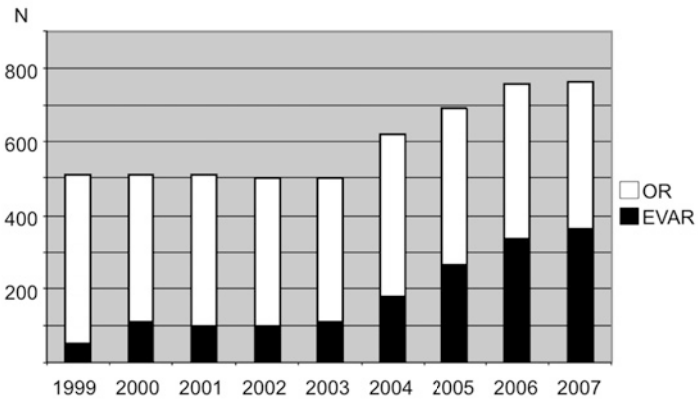


Figure 3. Number of elective AAA repairs in Sweden with open (OR) and endovascular (EVAR) technique (Swedvasc, 2008).

Since the introduction of EVAR in 1986 (Volodos, 1986; Parodi, 1991; Volodos, 1991), an increasing proportion of AAA patients are being treated with endovascular technique (Akkersdijk, 2004; Dillavou, 2006; Gibbons C, 2007; Wanhainen, 2008). Data from the Swedvasc indicate an increase of 53% in the total number of elective repairs and 189% in the number of EVARs in Sweden over the years 2003-2007, figure 3 (Swedvasc, 2008). In

2008, 53% of all elective AAA repairs in Sweden were performed with EVAR (Swedvasc, 2009).

### Ruptured AAA repair

The operative mortality after rAAA repair is approximately 35% (Wanhainen, 2008). However, only 1/3 of patients with AAA rupture undergo operation while the remaining patients die without surgical attempt. The overall mortality after AAA rupture is thus around 80% (The UK Small Aneurysm Trial Participants, 1998; Vardulaki, 1998). Some groups have reported stable mortality rate after rAAA repair (Heller, 2000; Wainess, 2004; Visser, 2005; Dillavou, 2006), whereas others have found a decreasing mortality over time (Bown, 2002; Cowan, 2006; Mureebe, 2008; Wanhainen, 2008). Endovascular repair for ruptured aneurysm is increasing and constituted 25% of all rAAA repairs in Swedvasc 2008 (Swedvasc, 2009). The feasibility of endovascular technique in an emergency setting has been established in several reports (Resch, 2003; Mehta, 2006). There is a great variety in use of EVAR for rAAA, and some centers treat a high proportion of all ruptures with this technique (Holst, 2009). However, it is difficult to compare the results of emergency EVAR to OR due to the effect of patient selection and the difficulty to perform randomized clinical trials in this acute setting (Hinchliffe, 2006). Large randomized clinical trials comparing OR and EVAR for rAAA are in progress (Hinchliffe, 2009).

## Screening

The best manner to avoid death in rAAA is timely operation of the aneurysm in the asymptomatic phase. However, most AAAs are undiagnosed and a majority of the patients with rAAA die before reaching the operation theatre (Bengtsson, 1993). Screening for AAA among individuals at risk could help identify aneurysms in time to offer preventive surgery.

In general, screening is regarded as an effective health measure when a set of basic criteria are fulfilled, table 1. Ultrasound screening for AAA fulfils all these criteria, and several well-performed randomized studies have shown that population-based screening of men aged 65 to 80 years reduces AAA related mortality with 48-67% in a cost-effective manner (Lindholt, 2006; Thompson, 2009). Currently, population-based screening is being implemented in the UK (Scott, 2008) and Sweden (Wanhainen, 2006; Swedish Council on Technology Assessment in Health Care, 2008).

In addition to population-based screening among men, screening for AAA in specific high-risk groups of individuals has been suggested (Beard, 2003; Earnshaw, 2004; US Preventive Services Task Force, 2005). Selective

screening of high-risk individuals is also reimbursed within the Medicare program in the United States (Lederle, 2008). A history of smoking is strongly associated with AAA (Cornuz, 2004) and has been suggested as a possible criterion for selective AAA screening (Lederle, 2003; US Preventive Services Task Force, 2005). Presence of atherosclerotic cardiovascular disease is also associated with a higher prevalence of AAA, and screening among these patients could potentially be beneficial. Other factors such as having a first degree relative with AAA or having a popliteal artery aneurysm are also significant risk factors for AAA and define proper high-risk groups for screening (Wanhainen, 2005; Ravn, 2007; Ravn, 2008). The prevalence of AAA in high-risk groups has been evaluated in several studies primarily in patients with cardiovascular disease and patients with heredity for AAA (Lindholm, 1985; Bengtsson, 1988; Bengtsson, 1989; Bengtsson, 1989; Nevelsteen, 1991; Bengtsson, 1992; Adams, 1993; Carty, 1993; MacSweeney, 1993; van Laarhoven, 1993; Eisenberg, 1995; Fitzgerald, 1995; Wolf, 1995; Kurvers, 2003).

Table 1. WHO criteria for a medical screening program to be acceptable (Wilson, 1968)

| | **Criteria** |
|---|---|
| 1 | The disease is an important health problem |
| 2 | There is a generally accepted treatment |
| 3 | Provisions for diagnosis and treatment are available |
| 4 | The disease must have a detectable latent stage |
| 5 | A suitable screening method must be available |
| 6 | The screening method must be accepted by the target population |
| 7 | The natural course of the disease must be known |
| 8 | The policy for the treatment of the disease must be clear |
| 9 | The cost-effectiveness of a screening program must be reasonable |
| 10 | The treatment of the disease should favor prognosis of patients |

Screening for AAA among patients with peripheral vascular disease who are referred to a vascular laboratory is an intuitive add-on to the vascular ultrasound imaging performed, and has been suggested in several reports (Carty, 1993; MacSweeney, 1993; Eisenberg, 1995; Wolf, 1995). However, the prevalence of AAA in different patient groups at a vascular laboratory has not been extensively studied. In addition, the long-term outcome and cost-effectiveness of this screening strategy need to be evaluated. While screening is ready at hand at a vascular laboratory, the comorbidity of general vascular disease in this patient group could affect the long-term survival negatively, and influence the cost-effectiveness of this screening strategy (Wanhainen, 2005).

# Health economics

Health economics is the study of how societies and individuals use their resources to promote health. The main purpose of health economic studies is to provide decision makers with solid information on how to reach an efficient use of the available resources in order to maximize the health of the population (Folland, 2007). Health economics has become increasingly important in health care decision making over the past decades. In some countries, health economic evaluation of new medications and treatment strategies is mandatory before these are reimbursed within the health care system (Jonsson, 2004; EUROMET, 2005). In vascular surgery, discussions on health economic benefits or costs of new endovascular techniques are common, and the number of publications in PubMed on cost for vascular surgical procedures has quadrupled since 1990, figure 4. Health economic evaluations are also important in preparation of screening programs for AAA, where considerations are made in order to maximize the benefit of the screening per Euro spent (Wanhainen, 2005).

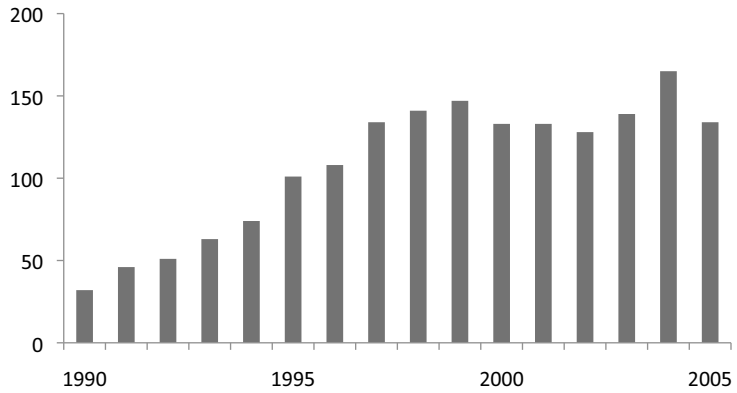


Figure 4. Number of publications registered in PubMed per year with the words "vascular surgery" and "cost" in abstract.

## Cost

All health interventions are associated with a cost. Cost of treatment can be divided into direct and indirect costs. Direct costs are directly linked to the treatment, detection, prevention or care of the patient (e.g. the cost of a stentgraft in treatment of AAA with EVAR). Indirect costs are costs that are related to consequences of an illness (e.g. the cost of sick leave for a patient who is not able to work for some time after AAA repair). When studying cost of a health intervention for the society as a whole, both direct and indirect costs should be considered. However, measurement of indirect costs is

often more difficult than compilation of data on direct cost of treatments. Therefore, many studies comparing cost of treatment with different modalities focus on analysis of direct costs (EVAR Trial Participants, 2005; Hayter, 2005; Prinssen, 2007).

As mentioned previously, use of EVAR has increased dramatically since the introduction of this minimally invasive technique. The introduction of a new technique is often associated with a cost, and an understanding of costs related to treatment, cost structure and cost differences between treatment modalities is important for adequate allocation of resources. It has been shown in studies from the United States, UK and Australia that cost of EVAR is higher than that of OR in patients available to both techniques, despite shorter hospital stay and ICU need after EVAR (Sternbergh, 2000; Dryjski, 2003; EVAR Trial Participants, 2005; Hayter, 2005; Prinssen, 2007). This is explained by the high cost of the stentgrafts. Cost of treatment is, however, highly dependent on health care system, price level and treatment practice and can therefore differ between countries (Brox, 2003). In addition, previous studies often focus on comparison of treatment cost for OR and EVAR in selected patient groups with similar clinical characteristics. The clinical situation where patients are selected for endovascular or open treatment based on age, aneurysm anatomy and patient co-morbidity is hence not reflected.

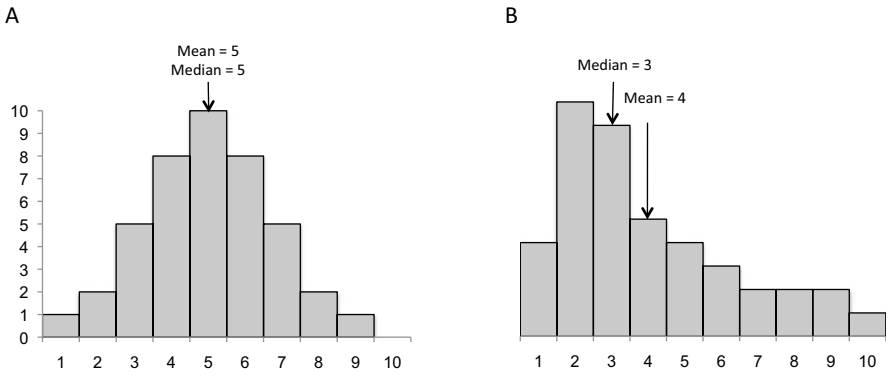


Figure 5. Schematic histograms illustrating the relationship of mean and median values to the total in a normal (A) and a skewed (B) distribution.

Statistical analysis of cost data poses specific challenges to the researcher. Cost data are almost always skewed, making it difficult to use normal statistical methods to analyze cost differences between alternative treatment strategies (Thompson, 2000). The median cost disregards the skewedness of data and, for example, underestimates the effect of seldom but regularly occurring cost-intensive cases and their effect on total resources needed over time,

time, figure 5. Thus, in contrast to other medical research areas where skewed data are best presented with median values, mean cost is a more relevant value to the economic decision maker e.g. in a budgeting situation.

Several inferential statistical methods exist for comparing cost of different treatment strategies, all having their pros and cons (Barber, 2000; Thompson, 2000; Rascati, 2001; Nixon, 2004; Thompson, 2005). Although several publications recommend a presentation of overall mean cost in health economic evaluations and statistically comparing data with parametric t-test or bootstrap technique (Barber, 2000; Thompson, 2000), there is no consistency in how cost data are analyzed and reported in the literature and the effect of different methodologies on interpretation of cost data has not been studied.

Table 2. Health utility index in different subgroups of the Swedish population as measured with the EQ-5D instrument (Burstrom, 2001).

| | **Utility index** | |
|---|---|---|
| | **Male** | **Female** |
| *Age groups, years* | | |
| 50-59 | 0.84 | 0.82 |
| 60-69 | 0.83 | 0.78 |
| 70-79 | 0.81 | 0.78 |
| 80-88 | 0.74 | 0.74 |
| *Disease groups* | | |
| Diabetes | 0.76 | 0.72 |
| Hypertension | 0.79 | 0.77 |
| Angina | 0.71 | 0.70 |
| Lower back pain | 0.64 | 0.68 |

## Effect

The effect of a health intervention is measured as the utility produced by the intervention. When a treatment results in a positive effect on overall survival, effect can be measured as life years gained (LYG) due to the health intervention (e.g. life years gained when one death due to AAA rupture is avoided). In addition to affecting survival, health interventions can also affect quality of life. Quality-adjusted life year (QALY) is a measurement of health effect that combines quality and quantity of lived life (Folland, 2007). Each year lived in perfect health is assigned the utility value of 1.0 QALY, down to the value of 0.0 for death. If an extra year gained due to a health intervention is not lived in full health (e.g. the patient loses a limb after ruptured AAA repair), the extra life years gained due to the intervention are given a value between 0 and 1 to account for this loss. There are two main methods for estimation of utility weighs of QALYs: standard gamble and time trade-off. Both these methods are based on peoples' preferences and

their willingness to trade between quality and quantity of life. The EuroQoL groups EQ-5D instrument is an example of an instrument that is widely used to measure utility weighs and renders a single index value for health status (Szende, 2004). The utility values for the Swedish population in different age groups have been established by means of EQ-5D, table 2 (Burstrom, 2001).

While QALY as measurement for effect has the benefit of including the aspect of quality of life, there are several limitations to this method. Use of QALY as effect measure inherently results in an undervaluation of life years saved in the elderly population, due to the lower QALY per lived year in this population compared to a younger and healthier population (Folland, 2007). Additionally, the QALY weight assigned to a specific health status can vary between individuals. Generally, healthy individuals underestimate the QALY related to a diseased health state compared to individuals afflicted by the disease (Folland, 2007).

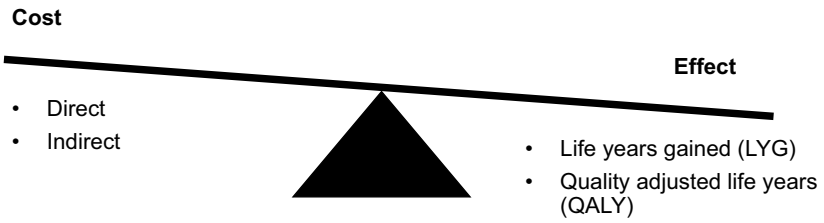


Figure 6. Health economic evaluation of cost and effectiveness.

## Cost-effectiveness

Economic evaluation, which is the largest area within health economics, compares costs and consequences of different health interventions in cost-effectiveness analysis, figure 6. The result of a cost-effectiveness analysis is expressed as cost per unit of clinical effectiveness, e.g. LYG or QALY gained.

Two alternative health interventions for a specific health state can be compared through cost-effectiveness analysis. The incremental cost-effectiveness ratio (ICER) which is calculated when comparing two interventions is defined as:

$$\mathrm{ICER} = \frac{\Delta C}{\Delta E} = \frac{C_1 - C_2}{E_1 - E_2}$$

where ΔC is the difference in total costs, and ΔE is the difference in effectiveness.

There are four main outcomes from a cost-effectiveness analysis. These can be illustrated in the cost-effectiveness plane, figure 7. A health intervention can be more costly and less effective than its alternative (A in figure 7), in which case it is never cost-effective. Similarly, an intervention can be less costly and more effective (D in figure 7), in which case it is always cost-effective. If a health intervention is more effective at a higher cost, or less effective at a lower cost (B or C in figure 7), the situation becomes more complex. Whether such an intervention is regarded as cost-effective or not depends on the willingness to pay for an additional gained unit of effectiveness. The willingness to pay threshold is represented by the dotted line in figure 7. A health intervention with a cost-effectiveness ratio in the shaded area to the right of and below the willingness to pay threshold is regarded as cost-effective.

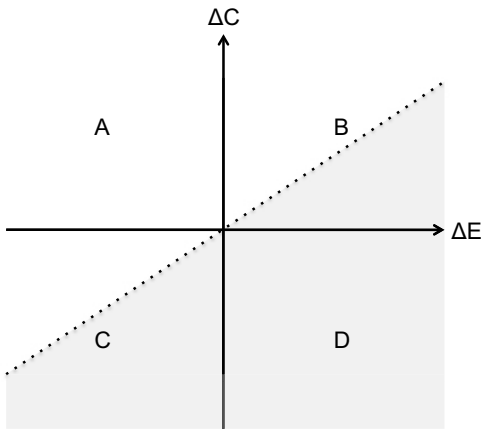


Figure 7. The cost-effectiveness plane. ΔC = difference in cost; ΔE = difference in effect. Dotted line = the willingness to pay threshold. The shaded area represents situations where outcome of the analysis is regarded as cost-effective.

The main advantage of the cost-effectiveness analysis is that it renders one single value that summarizes the costs and effects of a health intervention. It should however be underlined that the result of a cost-effectiveness analysis depends on the input data, both for cost (e.g. direct and indirect cost; treatment cost and future cost after initial treatment) and clinical consequences. In vascular surgery, cost-effectiveness analyses are used among others when studying the value of EVAR compared to OR and screening for AAA compared to non-screening.

The use of an acceptable threshold level for evaluation of the cost-effectiveness of a health care measure is attractive in its simplicity. How-

ever, there is no explicit threshold level that is ubiquitously accepted by policymakers when evaluating the cost-effectiveness of different health care interventions. The willingness to pay threshold is often based on the cost-effectiveness of the health care measures that the society has accepted to support in the current system. Dialysis care of end-stage renal disease patients is often quoted as having a very high cost per QALY (approximately €50,000 per QALY) and is used as the reference level for the willingness to pay threshold (Eichler, 2004). Some argue that the public acceptance for use of available resources on health care is even higher than this (Eichler, 2004). On the other hand, the National Institute for Health and Clinical Excellence in the United Kingdom uses a cost-effectiveness threshold range of £20,000 to £30,000 when evaluating new interventions (McCabe, 2008).

Cost-effectiveness analysis can in some cases be solely based on prospectively collected data in a randomized clinical trial when a health intervention is compared to an alternative intervention or non-intervention. It is also possible to perform cost-effectiveness analysis based on all relevant information about the consequences of the interventions. This combination of different sources of information is referred to as a modeling approach and often analyzes hypothetical populations in a computerized model. Such models can help informing decision makers on what strategy that is the most cost-effective based on current knowledge, which may not be captured appropriately in a clinical trial setting alone. There are different forms of modeling approaches to use in economic evaluations. Two of the most commonly used are decision-trees and Markov models.

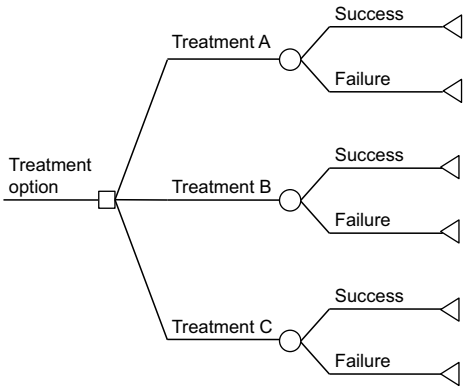


Figure 8. An example of a decision tree.

In decision tree models, different strategies are compared based on a number of possible outcomes and their expected probabilities and consequences, figure 8. However, decision trees do not easily permit recurring events or changing probability of events over time.

A Markov model is a cycle-based state-transition simulation model that can be used when a process occurs at a certain risk or with a changing probability over time, e.g. development of an AAA with a risk of rupture (Sonnenberg, 1993). Figure 9 shows an example of a Markov model. Markov model has been used for evaluation of different screening strategies for AAA (Lee, 2002; Boll, 2003; Henriksson, 2005; Wanhainen, 2005; Wanhainen, 2006). The model consists of a finite number of states of health (so-called Markov states, represented by circles in the diagram), and a patient is always in one, and only one, of these states. The time horizon of the analysis is divided into equal time periods of e.g. one year, referred to as Markov cycles. Arrows connecting two different states indicate allowed transitions, and an arrow leading from a state to itself indicates that the patient may remain in that state in consecutive cycles. The hypothetic patient moves through the Markov model in consecutive time cycles and transitions between health states take place based on the estimated probability of events, e.g. based on literature review. Each state is assigned outcomes, e.g. costs, life-years or QALYs.

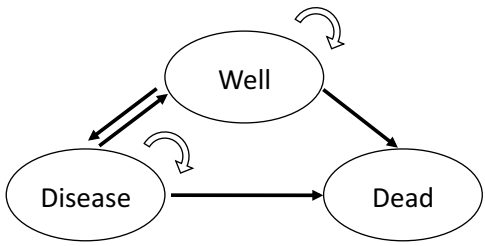


Figure 9. Bubble diagram of a simple Markov model.

In a Markov cohort simulation, a hypothetical cohort of patients beginning the process with some estimated distribution between the health states is modeled to go through the state transition diagram over a set of cycles. An important assumption of the model is that the probability of future events is only dependent on the current state of the patient, and not on the history of prior events. Outcome for this cohort simulation in terms of cumulative benefit and cost is compared between different strategies (e.g. screening and non-screening), and the ICER is calculated (Sonnenberg, 1993). The benefit of a Markov model analysis of cost-effectiveness is that different scenarios can be tested in a sensitivity analysis. In a one-way sensitivity analysis, the result of the model (e.g. the calculated ICER of a health intervention strategy) can be evaluated when one individual parameter in the Markov model is changed. Through this process, the effect of each parameter on outcome can be studied.

Monte Carlo simulation is another method sometimes used in modeling. Monte Carlo simulations can be first-order, in which each individual patient is followed through the model with retained memory of previous events, or second-order, in which the uncertainty of the underlying parameters in the model are taken into account in the model by allowing the parameters to vary over a given range with a given distribution (Briggs, 1998).

# Aims of the thesis

The overall aim of this thesis was to study epidemiological and health-economic aspects of AAA. The specific aims were:

To study the long-term survival after AAA repair (Study I)

To study time trends in the long-term survival among selected patient groups (Study I)

To study the cost of AAA repair in Sweden in a population-based setting (Study II)

To compare the cost structure of EVAR and OR in Sweden (Study II)

To review methods used in studies comparing cost of AAA treatment with EVAR and OR (Study III)

To study how different methods for presentation and analysis of cost data affect interpretation of results (Study III)

To study the prevalence of AAA in a selective screening setting at a vascular laboratory (Study IV)

To identify high risk groups with AAA in a selective screening setting at a vascular laboratory (Study IV)

To study the long-term outcome of AAAs identified in a selective screening program at a vascular laboratory (Study V)

To study the cost-effectiveness of selective screening for AAA at a vascular laboratory (Study V)

# Patients and methods

The studies conducted in this thesis are primarily based on subjects identified through national and local patient registries (the Swedvasc registry, the National Population Registry (NPR), the national registry of cause of death, local operation registries and local screening registries). Analyses of data based on these registries, patient records and hospital cost data form the basis for this evaluation of epidemiological and health economic aspects of AAA, table 3.

Table 3. Overview of patients and methods in the studies.

| | **Patients / materials** | **Methods** |
|---|---|---|
| Study I | 12,834 primary AAA repairs identified in the Swedvasc registry 1987-2005 | Analysis of crude and relative survival |
| Study II | 109 AAA repairs from the primary catchment area of Uppsala University Hospital 2001-2005 | Analysis of the cost of AAA repair and the cost structure for OR and EVAR |
| Study III | Same as study II; literature review of studies on cost of AAA repair 2003-2008 | Analysis of the effect of statistical methodology and presentation of data on interpretation of results of cost comparisons |
| Study IV | 5924 patients who had undergone selective screening for AAA at the vascular laboratory, Uppsala University Hospital, 1993-2005 | Analysis of the prevalence of AAA in selective screening, and multivariate logistic regression to analyze odds ratio for factors related to AAA |
| Study V | 181 AAAs identified through selective screening described in study IV; literature data on outcome of AAA used in health-economic modeling | Evaluation of the long-term outcome and analysis of cost-effectiveness in a Markov model |

## Study I

This analysis of the long-term survival after AAA repair was based on all primary AAA repairs registered in the Swedvasc 1987-2005. Survival data were obtained through crosschecking of the unique personal identification number (PIN) of each patient with the NPR in October 2007.

Crude- and relative survival was analyzed separately for patients operated on for iAAA and rAAA. Crude survival was calculated including all deaths. Relative survival was analyzed when excluding AAA repair-related mortality (Norman, 2001), defined as death within 90 days after surgery (Stenbaek, 2004; Laukontaus, 2006). Relative survival (Ederer, 1961) was calculated by comparing the observed survival (excluding operation related mortality) after AAA repair to the expected survival of the Swedish population adjusted for gender, age and calendar year. The expected survival was calculated by using life tables attained from the Human Mortality Database which includes death rates and life tables for national populations (The Human Mortality Database, 2008). Subgroup analyses were performed based on age, gender, comorbidities, time-period (1987-1999 vs 2000-2005), operative technique (OR vs EVAR), and operative volume. Center specific operative volume was analyzed for the period 1994-1999 and 2000-2005. Centers were categorized into three categories based on an arbitrary number of AAA repairs performed during each six-year period (low volume: in average <10 AAA repairs annually; medium volume: 10-25 AAA repairs annually; high volume: ≥25 AAA repairs annually).

## Studies II and III

These studies of the cost of AAA repair with OR and EVAR were based on a population-based cohort of all primary infrarenal AAA repairs (N=109) performed among patients from the primary catchment area of Uppsala University Hospital (304 367 inhabitants as of 31 December 2005) during the period 2001-2005. The analysis was based on intention to initial treatment and case-records were reviewed retrospectively.

In study II, clinical data were obtained from the Swedvasc registry and patient records. All pre-, peri- and postoperative hospital-related costs linked to AAA treatment were included in the cost analysis (mean of 2.5 years of follow-up). Cost was calculated based on the hospital's cost for each investigation according to the hospital's pricelist for diagnostics, treatments and interventions 2006 excluding margins, table 4.

To analyze the effect of statistical methodology on interpretation of results in study III, distribution of the cost data from the population-based study was displayed in box-and-whisker plots and histograms. Medians, means and confidence intervals (CI) were calculated for patients that had undergone OR and EVAR. The two groups were compared statistically using four different methods (student's t-test, Mann-Whitney U-test, logarithmic transformation and bootstrap technique, described in detail under the Statistics and ethics heading below). These methods were identified in a review of the statistical methods used in analysis of cost data in the PubMed indexed literature on cost of AAA repair 2003-2008.

Table 4. Specific medical costs.

| | Cost (Euro) |
|---|---|
| Stentgraft cost for EVAR (Cook Trifab)* | 7487 |
| Radiology cost for EVAR† | 1564 |
| Duplex scan | 214 |
| CT scan | 283 |
| Cardiology / pulmonary consultation | 117 |
| Echocardiography | 243 |
| Spirometry | 124 |
| Anaesthesia, per min | |
| Level 2-5‡ | 3.7 - 8.2 |
| Operation, per min | |
| Level 4-5‡ | 25.6 – 29.4 |
| ICU, per hour | 126 |
| Intermediate care, per hour | 85 |
| Ward care, per day 2006‡ | |
| Level 1 (Admission day) | 762 |
| Level 2 | 462 |
| Level 3 | 528 |
| Hospitalized rehabilitation, per day | 456 |

* Custom made devices have a higher cost that is charged separately and included in the cost analysis.

† Radiology cost for EVAR includes cost of radiology personnel, equipment and disposables other than the stentgraft used during the EVAR intervention.

‡ The levels correspond to the resource intensity of patient care based on set criteria, e.g. personnel need, rate of diagnostic investigations and medical therapy. Anaesthesia during EVAR was mainly priced as level 2-3, while OR was level 4-5. Ward care was level 1 at admission day for all patients (higher cost due to investigations performed at admission).

# Studies IV and V

Selective screening for AAA among patients referred for peripheral vascular examination was introduced as a clinical routine at the vascular laboratory of Uppsala University Hospital in 1993. This clinical routine was followed in approximately half of the patients during the first half of the study period, increasing to >80% of the patients later on. Patients with poor or no visibility to the aorta were not examined further unless there was a suspicion of aortic pathology. In study IV, all files in the vascular laboratory at Uppsala University Hospital were retrospectively reviewed. Between 1993 and October 2005 5924 subjects, primarily examined for peripheral arterial stenosis, had a minimum of one registered measurement of the infrarenal aorta and form the basis of this study, figure 10.

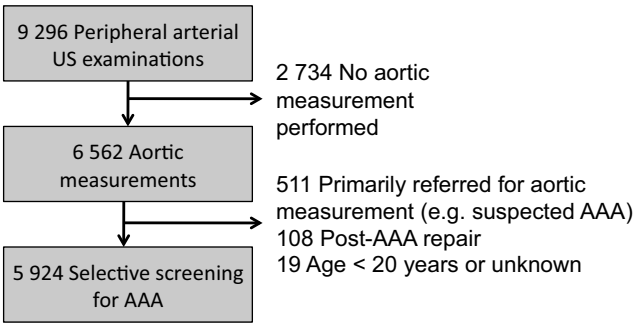


Figure 10. Peripheral arterial examinations and selective screening for AAA at Uppsala University Hospital 1993-2005. US = ultrasound.

Duplex scanning was carried out by experienced vascular technicians. The largest infrarenal abdominal aortic anteroposterior diameter was measured using the outermost ultrasonographic reflection with the transducer parallel to the longitudinal axis of the vessel. An AAA was defined as the maximum infrarenal anteroposterior aortic diameter ≥30 mm (McGregor, 1975). The carotid arteries, lower extremity arteries and the renal arteries were examined with both B-mode and color flow images.

In study V, patient records for all patients with a screening detected AAA were reviewed retrospectively. Patient comorbidities and follow-up examinations related to the detected AAA were recorded, as well as AAA-related interventions and their associated morbidity and mortality. Survival data and cause of death were obtained through crosschecking with the Swedish NPR and the cause of death registry. Relative survival and standardized mortality ratio (SMR) were calculated by comparing the observed survival of patients with AAA detected at selective screening to the expected survival of the entire Swedish population adjusted for gender, age and calendar year (Ederer, 1961).

The cost-effectiveness of a selective high-risk screening program in this setting (compared to non-screening) was assessed using a Markov cohort simulation model, figure 11 (Wanhainen, 2005). The cost (in Euro, 2006 year's value) per LYG was the main outcome measure and cost per QALY a secondary outcome measure. QALYs were estimated based on data from the general Swedish population (Burstrom, 2001). The willingness to pay threshold was set at < €50,000 per LYG (Eichler, 2004). Model probabilities were based on follow-up data from the present cohort, or from a literature review on outcome of AAA when necessary (Wanhainen, 2005), and were varied in a one-way sensitivity analyses.

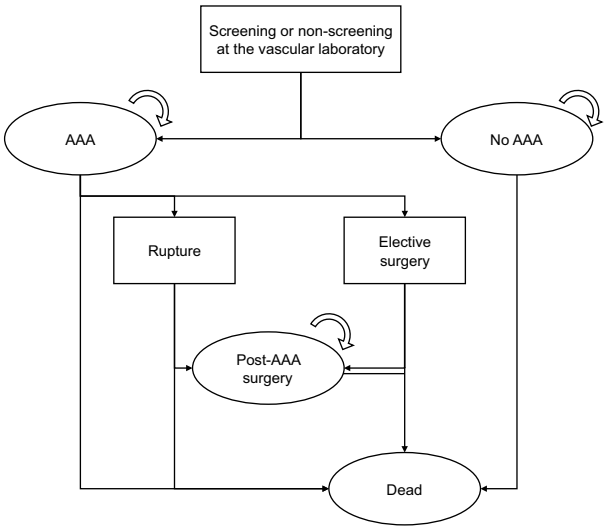


Figure 11. Markov model structure for screening vs non-screening for AAA at the vascular laboratory.

## Statistics and ethics

Statistical evaluation of the data was carried out with computer software packages (Stata 9, StataCorp LP, College Station, TX, USA for bootstrap analysis; TreeAge Pro 2007, TreeAge Software, Inc, Williamstown, MA, USA for health economic evaluation with Markov model; R Statistical Software Package, R Foundation for Statistical Computing, Vienna, Austria for relative survival analysis and SPSS PC version 14.0-16.0, SPSS, Chicago, IL, USA for all other statistical analysis). Independent samples t-test was used for comparison of normally distributed data. For comparison of two proportions, uncorrected Chi-square-test or Fisher's exact test were used. Standard deviation (SD) was calculated for mean data. Kendall's tau-b test was used to measure associations of ordinal variables. To estimate the odds ratio for factors in relation to AAA, multivariate logistic regression models were used. Crude survival was calculated with Kaplan-Meier analysis. Adjustments for multiple comparisons were made in study I: a p-value of $<0.01$ was considered significant and differences in survival between groups were analyzed with 99% CI. In all other studies, a p-value of $<0.05$ was considered as significant.

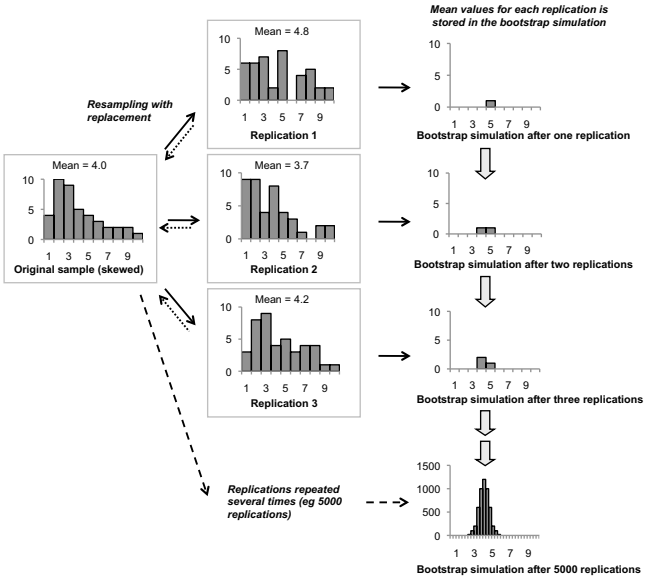


Figure 12. Schematic presentation of the bootstrap simulation technique.

The nonparametric bootstrap method was used for comparison of cost in studies II and III, figure 12. This is a method to simulate the distribution of the mean value of a skewed data set. A data set with N observations is resampled through random selection N times. After each randomization the selected observation is replaced and is thus at the same risk of being reselected at each randomization. At a formal level, an infinite number of resamplings are performed. In practice, the value of interest (e.g. confidence interval) often converges reasonably after thousand resamplings. The mean values from the resamplings are normally distributed and can be used in statistical analysis. The 95% CI of the mean is approximated using the 2.5 and 97.5 percentiles of the simulated data (Efron, 1998). Cost data were analyzed with three additional inferential statistical techniques in study III: independent samples t-test, Mann-Whitney U-test and logarithmic transformation. Mathematical transformation is used to achieve a more normal distribution of skewed data. This may enable the use of statistical tests that assume normality (e.g. Student's t-test) on skewed data sets (Altman, 1991).

All costs in the studies are presented in Euro 2006 values (1 Euro (€) = 1.3 US Dollars) updated using the Swedish Consumer Price Index (Swedish Consumer Price Index, 2006) and an average exchange rate between the Swedish Krona and Euro for the period 1/1/2006 to 30/6/2006 (OANDA, 2006).

Study I was ethically approved by the Swedvasc registry review board, which according to Swedish law has the authority concerning registry data. Studies II and III were based on retrospective analysis of patients' records and cost data in a single-center design and did not require ethical approval. Studies IV and V were approved by the Regional Ethics Committee of the Uppsala/Örebro region.

## Comments

The Swedvasc registry, which is one of the main sources of data for this research, is based on prospectively collected data and has nationwide coverage since 1994. The registry has been extensively validated both internally and externally, showing that core surgery (including AAA repair) is reported in more than 90% and with great validity of data (Bjorck, 1996; Bjorck, 2002; Kragsterman, 2006; Ravn, 2007; Swedvasc, 2007; Wanhainen, 2008). In a recent analysis (Troeng, 2008) the Swedvasc data registry was compared with the Swedish Hospital Discharge Register (for inclusion), and the NPR (for mortality) by matching every individual patient using the unique PIN. External validity for AAA-repair was 93.1%. In a hospital-specific analysis it was shown that non-registered procedures were localized to one non-compliant county hospital and small district hospitals that only performed rare emergency operations. Although there was a trend towards inferior outcomes after non-registered procedures, those were so few that in none of the analyses did the inclusion of non-registered procedures affect the general outcome significantly.

# Results

## Study I

In Study I, the long-term survival after AAA repair in Sweden over an 18-years long period was analyzed. Of 12 834 primary AAA repairs identified in the Swedvasc registry 1987-2005, 67.5% (n=8663) were performed for iAAA and 32.5% (n=4171) for rAAA. Survival data were obtained from the NPR in October 2007. Mean follow-up was 9.1 years (SD 4.6 years). Patient demographics changed over time, and patient characteristics differed based on gender, age and operative technique, as described in table 5. The proportion of iAAA repairs performed at high-volume centers increased from 61% in 1994-1999 to 73% in 2000-2005 (p<.001) and the use of EVAR for iAAA repair increased from 2.3% to 22.6% over the same time period. No endovascular rAAA repair was performed before year 2000. After 2000, 5.1% of all ruptures were treated with EVAR.

Table 5. Patient characteristics, study I.

| | Gender | | | Age | | | Time period | | | Technique† | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Male** | **Female** | **p** | **<80** | **≥80** | **p** | **1987-1999** | **2000-2005** | **p** | **OR** | **EVAR** | **p** |
| **iAAA (N)** | 7192 | 1471 | | 7697 | 966 | | 4886 | 3777 | | 2922 | 855 | |
| Mean age, years | 71.0 | 72.5 | <.001 | 69.9 | 82.1 | <.001 | 70.8 | 71.9 | <.001 | 71.2 | 74.3 | <.001 |
| ≥80 years, % | 10.3 | 15.1 | <.001 | - | - | - | 8.4 | 14.7 | <.001 | 11.7 | 25.0 | <.001 |
| Male % | - | - | - | 83.8 | 77.0 | <.001 | 83.5 | 82.3 | .141 | 81.3 | 85.7 | .003 |
| No comorb.* % | 30.8 | 39.3 | <.001 | 32.3 | 31.9 | .979 | 33.5 | 30.8 | .004 | 32.0 | 26.7 | <.001 |
| **rAAA (N)** | 3576 | 595 | | 3235 | 936 | | 2375 | 1796 | | 1705 | 91 | |
| Mean age, years | 72.5 | 76.1 | <.001 | 70.2 | 82.7 | <.001 | 72.5 | 73.7 | <.001 | 73.7 | 74.9 | .164 |
| ≥80 years, % | 20.5 | 33.9 | <.001 | - | - | - | 19.2 | 26.8 | <.001 | 26.2 | 37.4 | .028 |
| Male % | - | - | - | 87.9 | 78.4 | <.001 | 86.2 | 85.1 | .348 | 85.0 | 86.8 | .763 |
| No comorb.* % | 36.1 | 37.1 | .848 | 36.7 | 34.6 | .377 | 38.6 | 33.3 | .008 | 33.7 | 26.2 | .204 |

* No comorb. = proportion of patients with no registered cardiac, pulmonary, renal, diabetic or cerebrovascular disease

† Includes patients operated on 2000-2005.

### Survival after intact AAA repair

After iAAA repair crude 5-year survival was 69.0% (99% CI 67.7-70.4) and relative 5-year survival excluding 90-day mortality was 90.3% (88.6-92.0),

figure 13. Mean survival was 8.9 years (8.7-9.2). Short and long-term crude survival improved over time (1987-1999: 90-days 93.4% (92.5-94.3) 5-years 67.1% (65.4-68.9) vs 2000-2005: 90-days 95.6% (94.7-96.5), 5-years 72.2% (70.1-74.4), log rank p<.001), figure 14. Crude long-term survival was inferior for women at 10-years (women 33.8% (29.5-38.1), men 40.4% (38.5-42.3)) but there was no significant difference at shorter follow-up (log rank p=.013). Crude survival was lower for octogenarians (log rank p<.001), figure 15. There was no significant difference in crude 5-years survival between centers based on operation volume (low volume: 66.8% (61.1-72.5); medium volume: 71.1% (68.3-73.9); high volume: 69.4% (67.6-71.2)).

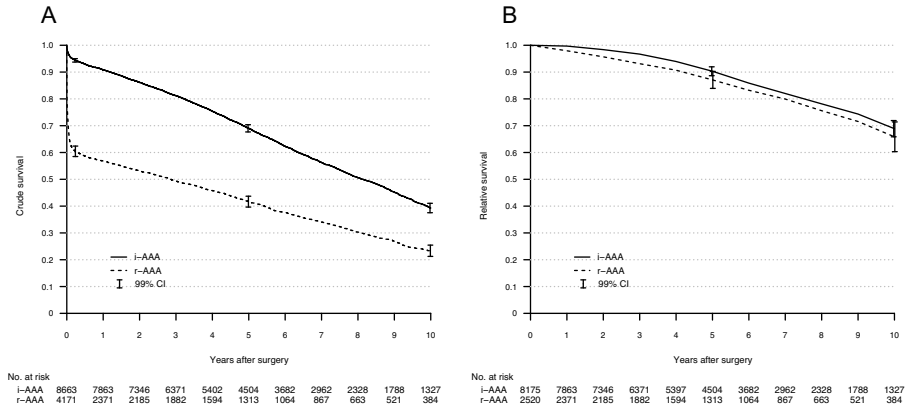


Figure 13. A) Crude survival after iAAA and rAAA repair. B) Relative survival excluding 90-day mortality after iAAA and rAAA repair.

Relative long-term survival excluding 90-day mortality was better for those operated on 2000-2005 compared to earlier, difference at 5-years (5yΔ) 4.7% (1.3-8.1), figure 14, and for octogenarians compared to patients <80 years of age, 5yΔ 10.2% (1.5-18.8), figure 15. No significant difference in relative survival was observed between other age groups (50-59 years, 60-69 years, 70-79 years). The relative survival benefit for patients ≥80 years compared to younger patient groups did not change over time and was observed irrespective of operative technique (OR/EVAR). Relative survival was lower for women compared to men, 5yΔ 4.6% (0.4-8.8) and 10yΔ 18.6% (11.1-26.1).

Survival after OR and EVAR was compared for the period 2000-2005 in order to compare contemporary results, figure 16. There was no significant difference in relative 5-year survival for patients alive at 90-days after iAAA repair when comparing OR to EVAR, Δ 6.0% (-1.5-13.4%). No significant difference in relative 5-year survival between EVAR and OR was observed when all patients were included in the relative survival analysis, i.e. when including 90-day mortality (EVAR 85.7% (78.9-92.5) vs OR 90.3% (87.4-

93.2)). Among patients ≥80 years of age, crude 90-day survival was significantly higher after EVAR (97.2% (94.3-100.1) vs OR (89.8% (85.5-94.0), but there was no significant difference in relative 5-year survival for patients alive at 90-days postoperatively (EVAR 96.9% (74.5-119.4) vs OR 104.7% (90.4-118.9)).

Relative survival decreased with increasing number of comorbidities (at 5-years, no comorbidities 93.6% (91.0-96.3); 1-2 comorbidities 83.2% (81.0-85.4); 3-5 comorbidities 59.0% (49,7-68.3)), figure 17A.

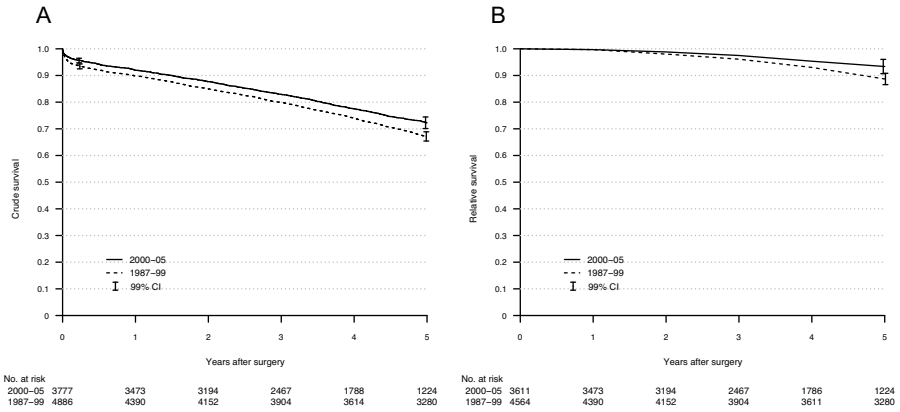


Figure 14. A) Crude survival after iAAA repair for operation period 1987-1999 and 2000-2005. B) Relative survival excluding 90-day mortality after iAAA repair for operation period 1987-1999 and 2000-2005.

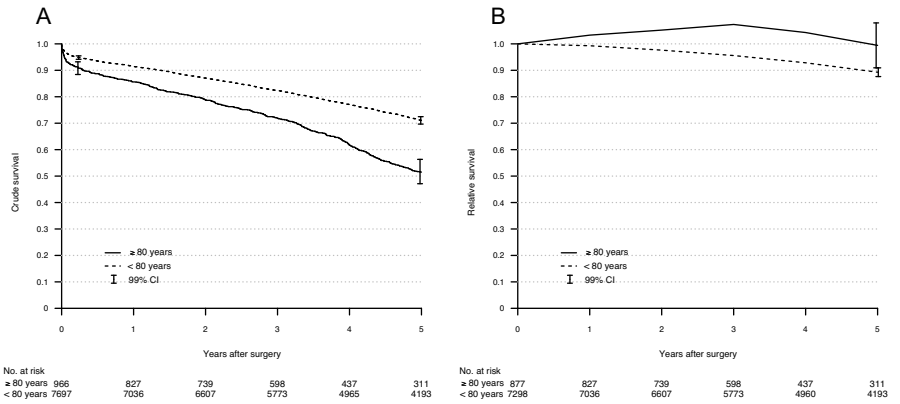


Figure 15. A) Crude survival after iAAA repair for patients <80 years and ≥80 years of age. B) Relative survival excluding 90-day mortality after iAAA repair for patients <80 years and ≥80 years of age.

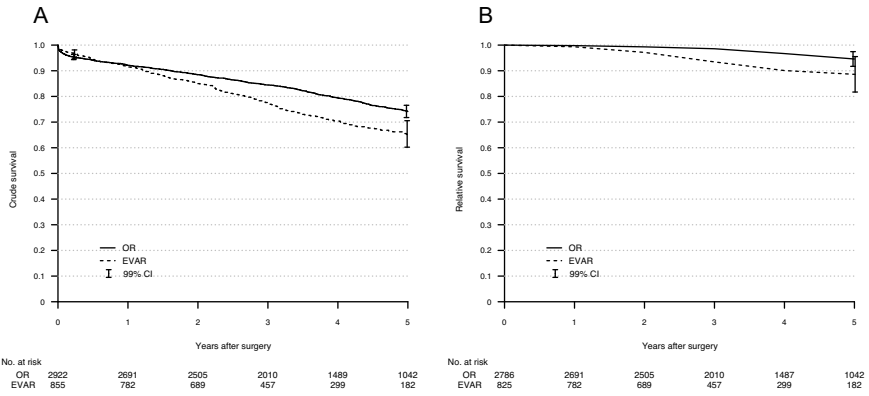


Figure 16. A) Crude survival after iAAA repair 2000-2005 for patients treated with OR and EVAR. B) Relative survival excluding 90-day mortality after iAAA repair 2000-2005 for patients treated with OR and EVAR.

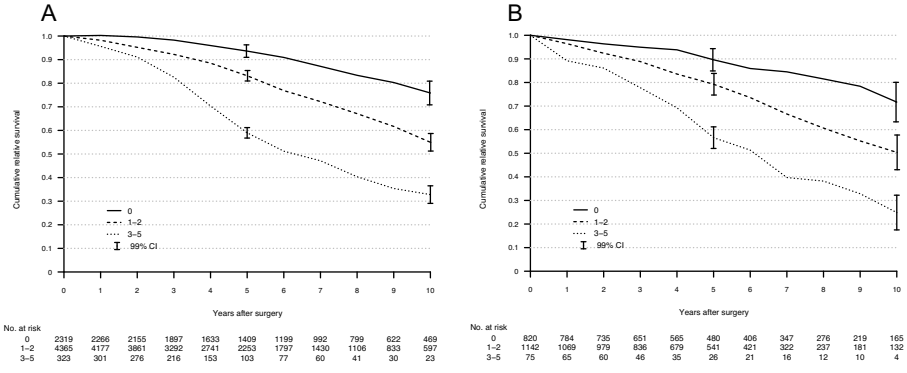


Figure 17. A) Relative survival excluding 90-day mortality after iAAA repair and B) after rAAA repair for patients with no comorbidity, 1-2 comorbidities and 3-5 co-morbidities.

## Survival after ruptured AAA repair

After rAAA repair crude 5-year survival was 41.7% (39.6-43.7) and relative 5-year survival was 87.1% (83.9-90.3), figure 13. Mean survival was 5.4 years (5.1-5.7). Short-term crude survival after rAAA improved over time but there was no significant difference in long-term survival (1987-1999: 90-days 57.8% (55.2-60.4), 5-years 40.0% (37.4-42.5) vs 2000-2005: 90-days 63.9% (61.0-66.8), 5-years 43.7% (40.4-47.0), log rank p=.001). Crude survival was lower for women (log rank p<.001), while no significant differences in crude 5-years survival based on center volume were observed (low volume: 38.7% (30.2-47.2); medium volume: 43.1% (38.7-47.5); high volume: 42.1% (39.3-44.9)).

Relative long-term survival among those surviving the operation for rAAA was not significantly lower after rAAA compared to iAAA repair, 5yΔ 3.2% (-0.4-6.8), figure 13. Relative long-term survival (excluding 90-day mortality) after rAAA did not improve significantly over time, and decreased with increasing number of comorbidities (at 5-years, no comorbidities 89.6% (84.9-94.3); 1-2 comorbidities 79.3% (74.7-83.8); 3-5 comorbidities 56.6% (37.7-75.5)), figure 17B. Relative survival was lower for women at 10 years, Δ 22.5% (5.5-39.4), but the difference was not significant at 5-years, Δ 5.6% (-4.4-15.6). There was no relative survival benefit for octogenarians compared to younger patients. As only 2.2% of all rAAA repairs were performed with EVAR, this group was not further analyzed.

## Comments

This study reports the development in long-term survival after AAA repair over two decades based on data from a national registry. The fact that every Swedish citizen has a unique PIN makes it possible to obtain 100% accurate survival data. Over the study period, several important changes in treatment of AAA repair took place (such as introduction of EVAR and improvement in postoperative care), and these developments resulted in increasing rate of repair among old patients with comorbidities. Despite this, the current analysis shows that in addition to improvements in short-term survival (Wanhainen, 2008), also long-term survival has improved over time. Thus, changes in patient selection and case-mix due to the current developments in AAA repair have not had a negative effect on long-term survival. Current selection of octogenarians for AAA repair also seems adequate, as the octogenarians who underwent AAA repair had a better long-term survival than the norm population matched for age, gender and calendar year. Long-term survival was not related to the operative technique. The improved long-term survival over time was most probably related to improvements in general cardiovascular care. Cardiovascular disease is the major cause of death among AAA patients (Johnston, 1994; Norman, 2001).

While short-term survival after rAAA repair increased over time, long-term survival was unaffected. The improved short-term survival would be expected to have an adverse effect on relative long-term survival when excluding perioperative mortality, if patients with more comorbidities survived rAAA repair during the later time-period. However, long-term survival after rAAA was stable suggesting that this effect may be balanced by a true long-term survival benefit.

The improved survival after iAAA repair has implications in clinical decision-making, as well as on health economic calculations, in particular related to different screening programs for AAA (Wanhainen, 2005; Wanhainen, 2006). The study's findings may however not necessarily translate to other countries. Differences in healthcare systems may affect patient

selection and outcome. As an example, higher rates of both elective AAA repair and EVAR are reported in North American studies compared to the current report (Heller, 2000; Wainess, 2004; Dillavou, 2006).

# Studies II and III

In Study II, cost of AAA repair in a population-based setting was analyzed, and in Study III, the cost data from this cohort were used to evaluate how different methods for presentation and analysis of cost data affect interpretation of results. In addition, a review of statistical methods used for analysis of the cost of AAA repair in the literature was performed.

## Patient characteristics

The clinical characteristics of the 109 elective AAA patients included in studies II and III are presented in table 6.

Table 6. Patient characteristics, studies II and III.

| | **Overall*** **N=109** | **OR** **N=58** | **EVAR** **N=51** | **p** |
|---|---|---|---|---|
| Age (year) | 72.8 | 69.7 | 76.3 | <0.001 |
| Aneurysm size (mm) | 61.1 | 61.6 | 60.6 | 0.651 |
| ASA | 2.4 | 2.3 | 2.6 | 0.025 |
| Cardiac disease | 58% | 48% | 69% | 0.035 |
| Pulmonary disease | 32% | 31% | 33% | 0.839 |
| Renal disease | 20% | 22% | 18% | 0.635 |
| Complex anatomy | 34% | 52% | 14% | <0.001 |

* All primary elective AAA repairs performed at Uppsala University Hospital 2001-2005 on patients from the Uppsala county region.

The rates of postoperative complications are presented in table 7. There was no 30-day mortality. One patient died after 37 days in the OR group. Two patients in the EVAR group were converted to open repair due to complications (one perioperative stent thrombosis and one stent dislocation). These patients were included in the EVAR group on an intention to treat basis.

## Cost and resources used

Overall, the mean total cost for an elective AAA repair including on average 2.5 years of follow-up was €28,193. The cost of AAA repair with OR and EVAR is presented in table 8.

Table 7. Re-operations and re-interventions after elective AAA repair, study II.

| | OR | EVAR | p |
|---|---|---|---|
| | n=58 | n=51 | |
| Re-operations or re-interventions during main hospitalization episode* | 19.0% | 13.7% | 0.607 |
| Any open re-operation | 19.0% | 7.8% | 0.104 |
| Any endovascular re-intervention | 0.0% | 5.9% | 0.099 |
| Re-operations or interventions during postoperative follow-up period | 12.1% | 13.7% | 1.000 |
| Open re-operations | 10.3% | 5.9% | 0.498 |
| Endovascular re-interventions | 1.7% | 9.8% | 0.096 |

* Frequency of patients requiring one or more re-operations or re-interventions. Includes patients converted from EVAR to OR as re-operated patients

Table 8. Cost of elective AAA repair in Euros, and p-values for comparison of cost of OR and EVAR with four different statistical methods. The results in Study II are based on comparison of mean cost with bootstrap technique (*in italics*).

| | | | P-value | | | |
|---|---|---|---|---|---|---|
| | **OR N=58** | **EVAR N=51** | **Bootstrap** | **t-test, mean** | **Mann-Whitney** | **t-test, log mean** |
| ***Total cost*** | | | | | | |
| *Mean* | *29,786* | *26,382* | *0.336* | 0.347 | 0.180 | 0.877 |
| Median | 19,876 | 22,183 | | | | |
| 95% CI Arithmetic | 23353 – 36218 | 23140 – 29624 | | | | |
| 95% CI Bootstrap | 24648 – 37139 | 23676 – 30017 | | | | |
| ***Preoperative cost*** | | | | | | |
| *Mean* | *661* | *1494* | *0.002* | 0.006 | 0.001 | 0.003 |
| Median | 400 | 1114 | | | | |
| 95% CI arithmetic | 363 – 959 | 984 – 2003 | | | | |
| 95% CI Bootstrap | 449 – 1041 | 1078 – 2087 | | | | |
| ***Perioperative cost*** | | | | | | |
| *Mean* | *24,512* | *20,484* | *0.135* | 0.172 | 0.524 | 0.442 |
| Median | 17 ,411 | 18,366 | | | | |
| 95% CI arithmetic | 19041 – 29983 | 18418 – 22550 | | | | |
| 95% CI Bootstrap | 20434 – 31127 | 18716 – 22634 | | | | |
| ***Postoperative cost*** | | | | | | |
| *Mean* | *4613* | *4403* | *0.209* | 0.901 | <0.001 | <0.001 |
| Median | 308 | 2588 | | | | |
| 95% CI arithmetic | 1826 – 7399 | 2546 – 6262 | | | | |
| 95% CI Bootstrap | 2340 – 7795 | 2940 – 6556 | | | | |

Total cost of treatment for one patient in the OR group exceeded 3SD above the mean total cost for patients treated with OR (mean €29,786, range €11,163 - €158,637). Total cost for EVAR cases was more homogenous (mean €26,382, range €13,067 - €78,562). Preoperative investigations and hospitalizations constituted 4% of the total cost, the main hospitalization and operation episode 80%, and the remaining 16% was cost related to postoperative investigations and hospitalizations. The higher preoperative cost

among EVAR patients was explained by a higher frequency of CT scans, angiograms and hospital care preoperatively (e.g. four EVAR patients underwent preoperative internal iliac artery embolization).

There was no significant difference in perioperative cost between OR and EVAR. However, the cost structure differed between the groups, with higher cost of ICU care in OR and higher cost of implants in EVAR (p<.001), figure 18. Average postoperative cost was similar in both groups. OR patients had a high postoperative cost the first year after operation, which dropped off thereafter, while EVAR patients had a more homogenous postoperative cost distribution over a five-year period, figure 19.

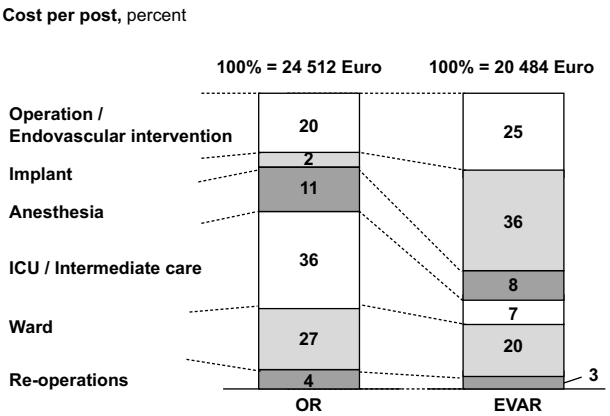


Figure 18. Cost distribution for elective OR and EVAR.

In order to evaluate the importance of age, comorbidity and anatomy as cost drivers, an analysis of overall treatment cost based on these factors was performed. Patients with complex anatomy had a higher perioperative cost compared to others (€27,790 vs €19,975, p=.009).

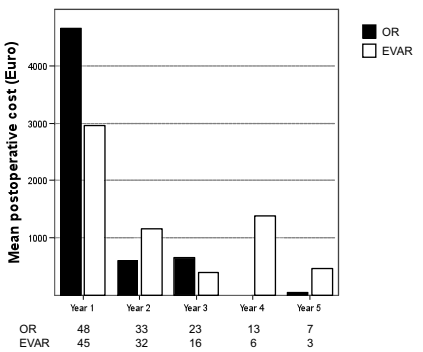


Figure 19. Follow-up cost after elective AAA repair.

## Statistical analysis of cost data

A review of the PubMed indexed literature 2003-2008 identified eleven articles assessing the cost of EVAR for AAA treatment compared to OR (Study III, page 3) (Dryjski, 2003; Watson, 2004; EVAR Trial Participants, 2005; Hayter, 2005; Rosenberg, 2005; Visser, 2006; Hynes, 2007; Prinssen, 2007; Lesperance, 2008; Mani, 2008; Tarride, 2008). A variety of methods were used for inferential statistics, and there was no consistency in how cost data were presented (means, medians, histograms, cost-effect plots). Handling of outliers also varied between reports. Only one study analyzed differences in cost of treatment between OR and EVAR with several separate statistical methods (Visser, 2006). There was however no discussion on the effect of statistical methodology on results of cost analysis.

Analysis of cost data from the population-based study in Uppsala County verified that all original cost data for AAA repair were highly skewed with numerous extreme values as visualized in box-and-whisker plots and histograms in figure 20 and table 8. Median cost was consistently lower than mean cost for both pre- peri- and postoperative cost of OR and EVAR, table 8. Mean and median values pointed in different directions in terms of what treatment strategy was least costly in three of four parameters (median cost lower for OR compared to EVAR in parameters total cost, perioperative cost and postoperative cost, while mean values were lower for EVAR in same parameters).

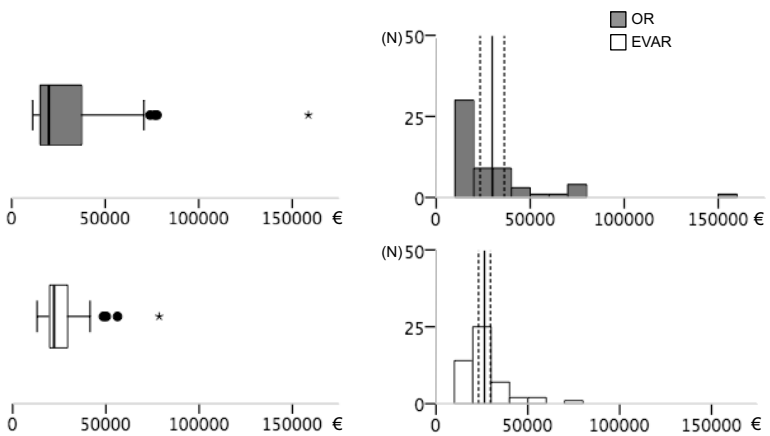


Figure 20. Box-and-whisker plots (left) and histograms (right) of total cost of elective AAA repair with OR and EVAR based on a population-based study. Box-and-whisker plots: the box indicates the interquartile range (IQR; leftmost line = lower quartile [Q1], mid line = median, rightmost line = upper quartile [Q3]); the whiskers indicate the smallest and largest non-outlier observations (within 1.5 IQR below Q1 or above Q3). • = Mild outlier (1.5-3 IQR below Q1 or above Q3). * = Extreme outlier (>3 IQR below Q1 or above Q3). Histograms: Each staple indicates the number of observations (N) in a specific cost interval. Full line = mean. Dashed lines = 95% confidence interval. € = Euro, N = Number of observations in each interval.

In order to test for the effect of extreme cost values in the dataset, mean values were calculated when excluding the only case with a mean total cost of treatment >3SD above the overall average. The case was a 73-years-old male with a 50 mm infrarenal aneurysm operated on with OR, and the extremely high cost was due to perioperative problems, postoperative hemorrhage and very long intensive care period. Exclusion of this case lowered mean total cost of OR by 8% (to €27,525), and mean perioperative cost for OR by 10% (to €22,161).

Results of inferential statistics with four different methods for the above-mentioned parameters are presented in table 8. P-values were homogenous irrespective of test method for one parameter (preoperative cost). There were large variations in p-value depending on test method for the other three parameters, and in one parameter (postoperative cost), two test methods indicated highly significant cost difference between OR and EVAR ($p<.001$), while two other methods did not indicate any significance at all ($p=.901$ and .209).

## Comments

These two studies conclude that cost of EVAR and OR is similar in a population-based setting when patients are selected for elective open or endovascular AAA repair based on aneurysm anatomy, patient age and comorbidity, whereas the cost structures of the two modalities differ significantly. The studies also highlight the importance of correct statistical methodology when analyzing cost data, and the inconsistency in methods used in the literature.

To verify the mean cost of elective AAA repair identified in this study, data were compared with the reimbursement level for AAA repair in Sweden and in the UK. The perioperative cost of AAA repair in the Study II was found to be in line with these comparisons. However, cost of OR in Study II was 68% higher compared to what was found in the EVAR 1 trial (€14,603 vs €24,512). This could be due to the fact that only about half of the patients in Study II matched the EVAR 1 trial criteria of being anatomically available for both EVAR and OR, and those not eligible were naturally more expensive to treat. The high rate of complex aneurysms and the subsequent high rate of complications and re-operations may explain the observed relative high cost of OR. Cost of EVAR was, on the other hand, relatively low considering the high rate of old patients with co-morbidities. Interestingly, overall treatment cost did not seem to depend on patient age or co-morbidities. Complex anatomy was, however, a significant cost driver due to higher operation-related costs and higher rates of complications.

Overall, cost data were skewed with an important difference between mean and median cost. Mean cost is the only relevant value to the decision maker, as median values underestimate the effect of seldom but regularly occurring complicated cases with extreme cost. These cases need to be ac-

counted for, e.g. in budget planning. For example, basing the budget for a unit performing 100 elective open AAA repairs annually on median cost would result in an underestimation of the budget with 30% in the current study example. Thus, in order to predict the overall cost, the most relevant value is the arithmetic mean.

Differences in mean cost are often best analyzed with the bootstrap technique (Thompson, 2000), and the two randomized studies included in the review used this technique for comparison of cost data for OR and EVAR (EVAR Trial Participants, 2005; Prinssen, 2007). While t-test would be an alternative to bootstrap analysis, p-values calculated with t-test and bootstrap were not always overlapping. Mann-Whitney U-test and logarithmic transformation of data are less applicable to cost comparison studies, as these two techniques do not focus on arithmetic mean cost.

In cost comparison studies, distribution of the data should be presented as thoroughly as possible, e.g. with means and confidence intervals. Interpretation of cost differences only based on significant p-values is hazardous, as the results of p-value analysis can be highly dependent on the method used. In addition, p-values do not reflect effect size, and even a highly significant p-value can be irrelevant in practice if the quantitative difference it refers to is small. When choice of statistical methodology is not obvious, such as in this form of cost analysis, an alternative can be to abstain from inferential statistics and present data thoroughly instead, or to sensitivity test statistical significance of differences in cost with several inferential methods.

# Studies IV and V

In Study IV, prevalence and risk factors for AAA were analyzed in patients who underwent screening for aneurysm when referred to a vascular laboratory for peripheral arterial ultrasound examination. Long-term outcome of patients with screening detected AAA in this setting was evaluated in Study V, and the screening was evaluated from a health-economic perspective.

## Prevalence of AAA

Of 5924 subjects screened, 55% were men. The mean age was 66.5 years (range 20-98) and the mean aortic diameter was 18 mm (range 7-82; men 19.3 and women 16.8, $p<.001$). An AAA was found in 179 subjects (78% men). The AAA prevalence was 4.2% (95% CI 3.5-4.9%) among all men and 1.5% (1.0-2.0%) among all women. Nineteen percent of AAAs in men was found among men younger than 65-years and 6% among men younger than 60-years. The corresponding proportions in women were 10% and 0%, respectively. Five aneurysms of 40-49 mm and six aneurysms of ≥50 mm

were found in men younger than 65-years, while no aneurysms ≥40 mm were found in women below 65.

Table 9. Adjusted odds ratio* for factors associated with AAA.

| | Adjusted odds ratio* (95% CI) | p |
|---|---|---|
| Male gender | 3.2 (2.2 - 4.6) | <0.001 |
| Age (per year) | 1.1 (1.0 - 1.1) | <0.001 |
| Age (per 10 years) | 1.7 (1.4 - 2.0) | <0.001 |
| Age (per 20 years) | 2.0 (1.6 - 2.6) | <0.001 |
| Any arterial stenosis | 2.0 (1.5 - 2.8) | <0.001 |
| Carotid artery stenosis | 2.3 (1.6 - 4.4) | <0.001 |
| Renal artery stenosis | 2.0 (1.1 - 3.6) | 0.019 |
| Extremity arterial stenosis | 4.5 (1.4 - 14.6) | 0.012 |

* Adjusted for male gender, age and arterial stenosis with AAA (or no AAA) as the dependent variable, in a logistic regression model. The different age intervals and stenosis locations were tested separately.

The primary target vessel for detection of peripheral arterial stenosis was the carotid arteries in 3772 subjects, the renal arteries in 1529 subjects and the lower extremity arteries in 1457 subjects. Among 5747 conclusive measurements a significant stenosis (>50%) in at least one location was found in 2169 (38%) patients. There was no difference in prevalence of stenosis between men and women (both 38%, p=0.97). The prevalence of arterial stenosis found at duplex increased with age, p<.001.

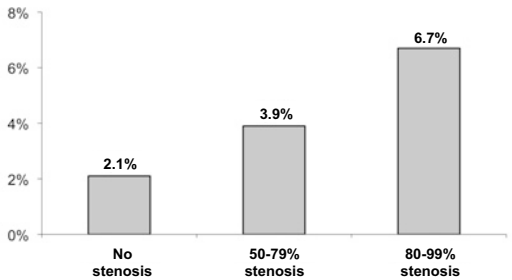


Figure 21. Prevalence of AAA in patients with or without carotid artery stenosis.

Table 9 displays adjusted odds ratio for the association between AAA and male gender, age and arterial stenosis in a multivariate analysis. The risk of having an AAA was significantly associated with the degree of carotid artery stenosis as shown in figure 21, p<.001. The prevalence of AAA in different subgroups depending on gender, age and presence of duplex-verified arterial stenosis are displayed in table 10. Patients with multiple verified stenoses had higher prevalence of AAA (no stenosis 2.1%, one stenosis 4.5%, two stenoses 7.3% and three stenoses 8.1%; p<.001).

Table 10. Prevalence of AAA depending on gender, age and duplex-verified arterial stenosis.

| Subgroup | | Men | | Women | |
|---|---|---|---|---|---|
| **Age (years)** | **Duplex-verified stenosis** | **No AAA / N (No AAA 30-39; 40-49; ≥50 mm)** | **AAA prevalence (95% CI)** | **No AAA / N (No AAA 30-39; 40-49; ≥50 mm)** | **AAA prevalence (95% CI)** |
| < 65 | No | 13 / 954 (9; 4; 0) | 1.4% (0.7-2.3%) | 0 / 688 | 0% |
| < 65 | Yes | 14 / 368 (7; 1; 6) | 3.8% (2.1-6.3%) | 4 / 247 (4; 0; 0) | 1.6% (0.4-4.1%) |
| ≥ 65 | No | 45 / 1022 (32; 10; 3) | 4.4% (3.2-5.8%) | 13 / 914 (9; 4; 0) | 1.4% (0.8-2.4%) |
| ≥ 65 | yes | 62 / 818 (47; 13; 2) | 7.6% (5.9-9.6%) | 22 / 725 (14; 6; 2) | 3.0% (1.9-4.6%) |

Among 9296 patients with arterial examination, 2734 did not undergo an examination of the aorta. In the later years screening was more prevalent than early. Between 1993 and 1999, 48% of the patients underwent screening of the aorta, while after 2000, 82% of the patients underwent aortic screening. The prevalence of AAA was, however, similar between the two time periods, 3% (2-4%) vs 3% (2-3%), p=0.61. Aortic measurement was more often performed among patients with arterial stenosis, especially early in the study period.

## Long-term outcome

In addition to the 179 patients with AAA identified in Study IV, two additional patients with an aortic diameter ≥ 30 mm in the selectively screened group were identified during the data collection process of study V. This rendered a total number of 181 patients with an AAA detected at selective screening forming the basis of study V.

After a mean follow-up of 7.5 years (SD 2.8) 47.5% of the patients were alive. Mean age at detection of AAA was 72.8 years, and mean AAA diameter 37.7 mm. Patients who later underwent elective repair of AAA were younger (66.5 vs 74.5 years, p<.001) and had larger aneurysms (44.1 vs 34.9 mm, p<.001) at detection compared to those who were not operated. Overall, 56.4% of the patients had an arterial stenosis on duplex examination and 64.8% had registered cardiac comorbidity at time of screening.

One hundred six patients (59% of all patients with a screening detected AAA) underwent surveillance. In 75 patients (41%) no surveillance was initiated. In eleven of these a poor general health was explicitly mentioned as the cause not to follow-up the patient further. Most of the remaining patients were old and had small aneurysms. Mean estimated cost of resources used for follow-up per patient was €1579. Mean survival was 8.3 years (95% CI

7.4-9.3) and 5-year survival was 63.3% (95% CI 56.0-70.6). Relative 5-year survival for the entire patient group was 80.4% (95% CI 70.8-88.8). The SMR was 2.0 (95% CI 1.5-2.5). Cardiovascular disease was the major cause of death in this patient group, accounting for 67% of all deaths. A total of six registered ruptures occurred in the cohort, which equals a 0.6% rupture risk per year.

Thirty-nine patients (21.5%) underwent elective AAA repair. Twenty-seven patients underwent open, eleven endovascular and one a hybrid repair. There were two perioperative deaths, one death after hybrid repair of a thoracoabdominal aneurysm and the other after open repair of a pararenal aneurysm (5.1% perioperative mortality). Mean time from screening to elective AAA repair was 2.8 years (SD 2.6). Nine patients (5.0% of all screening detected AAAs) underwent elective repair within six months from screening. Among men with a duplex-verified arterial stenosis the AAA-prevalence was 6.5% (78/1197), of whom 28.2% (n=22/78) underwent elective repair. The corresponding figures for men without stenosis was 2.9% (58/1976) and 12.1% (n=7/58), for women with a stenosis 2.7% (26/972) and 19.2% (n=5/26), and for women without stenosis 0.8% (13/1602) and 15.4% (n=2/13).

## Economic evaluation

The incremental cost-effectiveness ratio of a screening program compared to non-screening was €11,084 per LYG. The main cost driver in screening was the cost of elective repair of detected AAAs, table 11. Cost per QALY gained was €14,762 in the base-case. The cost per QALY gained increased to €19,683 in the scenario assuming a general reduction of quality of life by 25% in the whole population, and non-screening was the dominant strategy when assuming a 10% reduction in quality of life for patients with known un-repaired AAA (i.e. screening was associated with an incremental cost and a decrease in QALYs). The effect of the different parameters on ICER is presented in the sensitivity analysis in table 12. The ICER increased exponentially at very low levels of AAA prevalence, figure 22.

Table 11. Base-case cost of screening for AAA among patients referred for arterial duplex examination, per person in Euro.

| | Non-screening | Screening | Difference |
|---|---|---|---|
| Screening | 0.0 | 4.0 | 4.0 |
| Follow-up | 19.5 | 48.4 | 28.9 |
| Elective repair | 62.5 | 154.0 | 91.6 |
| Ruptured repair | 63.6 | 25.1 | -38.5 |
| Follow-up after AAA repair | 15.6 | 31.2 | 15.5 |
| Total cost | 161.2 | 262.7 | 101.5 |

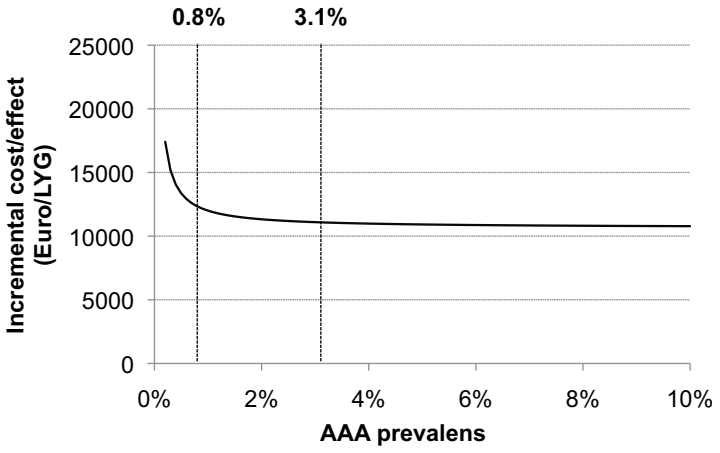


Figure 22. Incremental cost effectiveness of selective screening based on varying prevalence of AAA. The dashed lines represent prevalence of AAA in women without stenosis (0.8%) and in the selective screening population as a whole (3.1%).

Table 12. One-way sensitivity analysis of Markov model, per person in Euro.

| | Assump-tion | Cost differ-ence* | Differ-ence in life years* | Cost per life year gained* |
|---|---|---|---|---|
| Base case | - | 101.53 | 0.0092 | 11,084 |
| AAA prevalence | | | | |
| Women without stenosis | 0.8% | 29.17 | 0.0024 | 12,339 |
| Women with stenosis | 2.7% | 88.95 | 0.0080 | 11,148 |
| Men without stenosis | 2.9% | 95.24 | 0.0086 | 11,114 |
| Men with stenosis | 6.5% | 208.50 | 0.0192 | 10,855 |
| AAAs yearly risk of non-ruptured repair, screened group | 1.0% | 18.00 | 0.0093 | 1941 |
| | 3.9% | 129.04 | 0.0091 | 14,141 |
| AAAs yearly risk for non-ruptured repair, non-screened group | 0.5% | 140.47 | 0.0094 | 14,949 |
| | 2.0% | 77.42 | 0.0090 | 8594 |
| Mortality for non-rupture AAA repair | 2.7% | 101.62 | 0.0093 | 10,946 |
| | 3.6% | 101.46 | 0.0091 | 11,197 |
| Ruptured AAA total mortality | 71% | 100.71 | 0.0082 | 12,353 |
| | 84% | 102.04 | 0.0098 | 10,423 |
| AAAs yearly risk of rupture, screened group | | | | |
| | 0.4% | 92.57 | 0.0124 | 7475 |
| Registered ruptures, current report | 0.6% | 97.10 | 0.0108 | 9024 |
| Assuming 10% miss-diagnosis of ruptures as cardiac deaths in current report | 1.3% | 112.22 | 0.0053 | 21,305 |
| | 1.7% | 120.38 | 0.0023 | 53,341 |
| AAAs yearly risk of rupture, non-screened group | 1.4% | 115.31 | 0.0051 | 22,798 |
| | 2.4% | 88.45 | 0.0131 | 6748 |
| Proportion of rAAA operated | 30% | 116.92 | 0.0092 | 12,764 |
| | 70% | 86.14 | 0.0092 | 9404 |
| AAA patients' relative long term mortality | 1.4 | 108.88 | 0.0123 | 8867 |
| | 3.0 | 92.29 | 0.0063 | 14,652 |
| Cost of screening | 0 | 97.53 | 0.0092 | 10,647 |
| | 60 | 157.53 | 0.0092 | 17,197 |
| Cost of follow-up, per year | 200 | 93.49 | 0.0092 | 10,206 |
| | 400 | 114.37 | 0.0092 | 12,485 |
| Cost of non-ruptured AAA repair | 19 580 | 89.20 | 0.0092 | 9737 |
| | 25 674 | 113.86 | 0.0092 | 12,429 |
| Cost of repair for rAAA | 1.3x elective | 106.66 | 0.0092 | 11,644 |
| | 4.0x elective | 37.41 | 0.0092 | 4084 |

* Screening compared to non-screening.

## Comments

This is one of the largest studies of selective screening for AAA ever reported (Lindholm, 1985; Bengtsson, 1988; Bengtsson, 1989; Bengtsson, 1989; Nevelsteen, 1991; Bengtsson, 1992; Adams, 1993; Carty, 1993; van Laarhoven, 1993; Eisenberg, 1995; Fitzgerald, 1995; Wolf, 1995; Kurvers, 2003; Derubertis, 2007). The results of Study IV were consistent with previous reports that male gender, high age and the presence of arterial stenosis were all significantly and independently associated with AAA. Lower extremity arterial stenosis was associated with the strongest odds ratio for AAA in the logistic regression model, and there was a dose-response relationship between degree of carotid artery stenosis and prevalence of AAA.

Study IV found an AAA prevalence of ≥3% in men below 65 years with duplex-verified arterial stenosis, all men above 65 years of age and women above 65 years of age with duplex-verified arterial stenosis. These groups of patients may be regarded to have a sufficient risk of having an AAA to potentially justify screening from a prevalence point of view. While screening among high-risk individuals has been shown to reduce aneurysm-related mortality (Lindholt, 2007), the cost-effectiveness of selective screening of high-risk groups could be questioned. Patients with peripheral arterial disease would be expected to have a shorter life expectancy than the general population, as well as a potentially lower quality of life and a higher perioperative mortality and comorbidity rate than the average AAA patient, all of which reduces the benefit of treating an AAA.

In Study V health economic support was found for screening for AAA among patients referred to a vascular laboratory due to suspected arterial disease. Despite a high frequency of comorbidities and low relative survival, selective screening for AAA was cost-effective. In addition, the sensitivity analysis showed that screening was cost-effective for all patient subgroups (men and women with and without stenosis) despite a very low prevalence of disease in certain groups. There was only a small health economic benefit for screening with increasing prevalence of AAA above a threshold level of ~1%. The main economic difference between screening and non-screening was due to the cost of follow-up and repair of AAAs identified through screening.

A lower proportion of the patients with a detected AAA were operated on electively in this study (3.5% per year) compared to what has been reported in previous randomized screening trials of the general male population (5.1-6.5% per year (Ashton, 2002; Lindholt, 2005)), and a large proportion were not followed-up despite that a small AAA was detected at screening. The fact that screening may have been performed in patients not regarded as suitable candidates for follow-up, nor for surgery, is ethically questionable. However, in the clinical setting, the risk-benefit analysis is made on an individual basis. It is possible that some patients who were not candidates for

follow-up for a small AAA would have been regarded to benefit of repair if they had had a large AAA at screening.

The incremental cost-effectiveness of screening compared to non-screening surpassed the willingness to pay threshold under two circumstances: 1) when assuming a very high rupture rate in the screened population and 2) when assuming a decreased utility in patients with a known AAA (the latter resulting in lower total QALY and higher cost). There are not enough data on effect of AAA screening on quality of life to assume a consistent reduction in utility solely due to the knowledge of having an AAA (Ashton, 2002; Spencer, 2004; Wanhainen, 2004; Brannstrom, 2009). Still, the drastic effect of a hypothetical 10% decrease in utility after AAA detection on the health economic value of screening points out the importance of this field for further studies.

There are important limitations to these two studies. These include the lack of reliable data on smoking habits and the fact that 1/3 of the patients at the vascular laboratory did not have an aortic measurement. Smoking is a potential confounder that would have been most interesting to study in relation to AAA prevalence and atherosclerosis. The fact that not all patients were screened for AAA introduces a potential selection bias. However, while the proportion of patients screened increased over time, the overall prevalence of AAA did not change. In addition, the retrospective nature of the study and lack of a randomized non-intervention comparison group makes the health-economic evaluation of the selective screening strategy partly dependent of literature data. However, the sensitivity analysis performed in the health economic evaluation allowed us to assess the effect of the uncertainties introduced by the above-mentioned limitations.

# General discussion

The treatment of AAA has changed dramatically since the first repairs performed in the 1950's. Development has been observed in several areas. Diagnostics is ever improving with new ultrasound equipment and computed tomography with possibility for multi-planar and three-dimensional reconstruction for operation planning. In the treatment area, endovascular techniques are now established for repair of AAA and are continuously refined. In pre-, peri- and postoperative care, knowledge has improved on when to operate, how to optimize the patient for intervention, how to treat complications and what follow-up to plan. With improved diagnostics, refined techniques, and better outcome, AAA repair is being offered to more patients. Introduction of screening for AAA will increase this activity further, and will hopefully radically reduce the number of AAA related deaths in rupture. With these trends in mind, it is desirable to further improve results in terms of perioperative mortality and long-term survival. In the current economical climate with strong focus on how the limited financial resources are used in health-care, the case for an increase in activity in diagnosing and treating AAA should be based on solid health-economic calculations, which show that such use of resources is cost-effective.

## Outcome of AAA repair – can the results be further improved?

The short- and long-term survival after AAA repair has improved substantially over the past decades. Improvements in short-term survival have been shown in studies from the USA and Sweden (Cowan, 2006; Dillavou, 2006; Wanhainen, 2008). The perioperative mortality rate for iAAA repair in Sweden decreased from 10% in historical cohorts (Liljeqvist, 1979) to 4.7% in 1994-1999 and 3.2% in 2000-2005. Historically, the decreasing mortality was probably due to improved perioperative care. The most important factor for improvement in the latter period was the introduction of EVAR (Wanhainen, 2008). The 30-day mortality after rAAA repair also improved over time (from 38.4% in 1994-1999 to 32.9% in 2000-2005, p=.001), mainly due to improvement in survival after open surgery for ruptured AAA. Study I in the current thesis showed that also long-term survival after iAAA

repair has improved. This is not only good news for patients and physicians; it also justifies the increased activity in detection and treatment of AAA also among elderly patients as well as among those with comorbidities. Furthermore, this finding increases the health-economic value of an extended surgical activity. Can short- and long-term outcome after AAA repair be expected to improve further over the coming years?

## The role of EVAR

The short-term mortality among patients operated on with EVAR was considerably lower than after OR in a nation-wide study based on Swedvasc data (2.5% for EVAR vs 4.1% for OR, p=.015) (Wanhainen, 2008). In 2005, 35% of all iAAA repairs in Sweden were performed with EVAR. EVAR is, however, more common today and recent studies show that >50% of all AAA repairs in the USA and up to >70% of all iAAA repairs at certain centers are performed with EVAR (Giles, 2009; Vogel, 2009). In Sweden, more recent data from 2008 shows than half of the iAAA repairs were performed with EVAR (Swedvasc, 2009). Further dissemination of EVAR could help improving the short-term outcome of AAA repair at centers with low endovascular activity today.

Published randomized trials and national data indicate a perioperative mortality rate for EVAR of approximately 2% (Greenhalgh, 2004; Prinssen, 2004; Wanhainen, 2008). However, recent data presented from the ongoing US-based OVER trial indicate a perioperative mortality rate of only 0.5% (Lederle, 2009). This lower perioperative mortality could have several potential explanations; the OVER trial includes patients with AAA >5.0 cm, which is a lower size limit than the current practice of treating AAAs >5.5 cm in Europe, thus patient selection might affect the results. Additionally, the patients in the OVER trial had better cardiovascular preventive treatment with statins and betablockers compared to what has been reported from previous randomized trials. As previously discussed, national differences exist in perioperative mortality after AAA repair, and could affect outcome. It is also possible that increased experience with EVAR and the availability of newer devices have resulted in improved survival. Due to the randomized setting of the trial with selection of patients with favorable anatomy, available for both OR and EVAR, it is difficult to compare the results of the OVER trial with outcome in national databases such as the Swedvasc.

The feasibility of EVAR in the acute setting has been shown in several studies (Resch, 2003; Dillon, 2007), and there are indications that short-term outcome after rAAA repair is superior with EVAR compared to OR (Moore, 2007; McPhee, 2009). The initiated IMPROVE trial, which is a randomized controlled trial comparing OR to EVAR for rAAA, will hopefully result in evidence to evaluate the possible use of EVAR in the acute setting (Hinchliffe, 2009). In this trial, patients are randomized to open or endovas-

cular repair of a ruptured aneurysm already upon suspicion of rAAA, ie before any imaging is performed. Thus, the potential negative effect of delay for imaging among rAAA patients is included in the study. With this study, the role of an EVAR-first strategy in treatment of rAAA can be evaluated.

While EVAR has the potential to improve short-term survival after AAA repair, it is unclear whether this short-term benefit is sustained in the long-term. The randomized clinical trials comparing OR and EVAR among patients available for both techniques did not find any difference in total mortality in the long-term, while aneurysm-related deaths were fewer in the EVAR group compared to OR (Blankensteijn, 2005; EVAR Trial Participants, 2005; Lederle, 2009). Long-term survival after AAA repair was similar for OR and EVAR in propensity-score matched cohorts of Medicare beneficiaries undergoing repair 2001-2004 (Schermerhorn, 2008), as well as in Study I. However, the lack of data on aneurysm morphology in these two retrospective studies is a significant limitation.

Introduction of EVAR has made treatment of AAA possible in older patients and in those with severe comorbidities (Schwarze, 2009). This is reflected in an increase in workload of AAA repairs (Wanhainen, 2008; Giles, 2009). The current change in patient mix has not had a negative effect on short- or long-term survival after AAA repair (Study I; Wanhainen, 2008; Giles, 2009). However, continuous change in patient selection warrants further study of long-term results after AAA repair in the future (Schwarze, 2009).

## Improved medical treatment

As discussed earlier, improved secondary preventive treatment of cardiovascular disease is probably the most important factor behind the improved long-term relative survival after AAA repair found in Study I. Previous studies show that mortality after myocardial infarction in Sweden decreased drastically in the last decade (Norhammar, 2007). During the same period, the use of preventive medications such as statins and ACE-inhibitors increased significantly (Walley, 2004; Bjorck, 2007; Norhammar, 2007). The improved long-term results of the OVER trial compared to previous randomized trials might be related to the higher use of betablockers and statins (Lederle, 2009).

Adequate medical treatment is important for survival of AAA patients both in short- and in long-term. Patients with AAA have a significant cardiovascular comorbidity (Hertzer, 1984), and cardiovascular disease is the most common cause of death in this patient group (Johnston, 1994). Preoperative use of statins reduces the risk of perioperative death in this patient group, as well as having cardiac protective effect in the long-term (Schouten, 2009). Additionally, there are some indications that statins might reduce the expansion rate of small AAAs, and their role in a screening setting among

patients with small AAAs merits further investigations (Baxter, 2008; Van Kuijk, 2009). Use of beta-blockers for improvement of perioperative outcome is debated (Poldermans, 1999; Devereaux, 2008; Van Kuijk, 2009).

## Gender differences

Overall, 16% of all AAA repairs in Study I were performed in women. This is in line with international reports (Gibbons C, 2007). The 30-day mortality rate after iAAA repair was higher for women compared to men in a previous analysis of Swedvasc data (Wanhainen, 2008). The effect of gender on perioperative outcome after AAA repair is difficult to assess. The higher perioperative mortality for women might be related to the higher age in this group of patients, as increased age obviously affects survival negatively (Hultgren, 2007; Larsson, 2008). However, other studies indicate worse perioperative outcome for women despite corrections for other factors (Dillavou, 2006; Wanhainen, 2008; Abedi, 2009).

The inferior long-term survival in women found in Study I was consistent with previous reports (Norman, 1998; Hultgren, 2007). The increased mortality among women could be related to increased cardiovascular morbidity in female AAA patients (Norman, 1998), as well as worse outcome of cardiovascular disease in women (Pilote, 2007). There are also indications that female patients might have an increased long-term mortality in aneurysm-related deaths and that the prevalence of aneurysm disease in other parts of the aorta are more common in women than in men (Hultgren, 2007).

As discussed earlier, EVAR is associated with a lower short-term mortality than OR. There are indications that female AAA patients are less frequently suitlable for EVAR than men, due to more challenging anatomy (smaller iliac vessels, more angulated aneurysm necks) (Carpenter, 2001; Velazquez, 2001). In Study I, EVAR was used less frequently for iAAA repair among women than among men (EVAR was used in 18% of all iAAA repairs among women 2000-2005 compared to 24% of iAAA repairs among men during the same time period (p=.003)). Some investigators have reported a higher perioperative mortality after EVAR in women compared to men (Harthun, 2008; Abedi, 2009).

Women with AAA have a higher risk of rupture compared to men (Brown, 1999; McPhee, 2007; Abedi, 2009). Screening for AAA among women could help identifying the disease early. Although there is no strong evidence to support such screening, it is possible that AAA screening among women or at least in selected female populations is cost-effective despite the low prevalence of disease (Wanhainen, 2006; Derubertis, 2007). A screening-study of 70-year old women in two Swedish regions (counties of Uppsala and Dalarna) will be completed by late 2009.

## Centralization

High surgeon and hospital volumes have been shown to correlate with better perioperative outcome in AAA repair (Holt, 2007; Young, 2007). Surgeon specialty is also related to outcome, in the sense that vascular surgeons have better results than general surgeons, which of course is expected (Basnyat, 1999; Dimick, 2003). There has been a trend towards increased centralization of AAA repairs in Sweden over the past decades, and the proportion of iAAA repairs performed at high-volume centers (defined as centers performing ≥25 AAA repairs annually) increased from 61% in 1994-1999 to 73% in 2000-2005 in study I ($p<.001$). It would be of interest to analyze how this increased centralization correlated with perioperative outcome in the studied cohort. Centralization did however not affect long-term survival in study I. An important issue is if the critical threshold for good results can be identified. It seems clear from the literature that centers regularly performing less than 10 AAA procedures per year should consider referring all patients to high-volume centers instead (Troeng, 2008). When evaluating the high-volume centers (>50-100 procedures/year), the analysis is complicated by referrals, as those patients are often high-risk patients.

With the increasing use of EVAR, number of open repairs is decreasing at the same time that there is a selection of cases with complex aneurysm anatomy to OR. Due to these two trends, it is possible that there will be an increasing need for further centralization of open aortic surgery in the future.

## National differences

There are important national differences in short-term outcome after AAA repair. An international comparison of outcome of AAA repair based on national vascular surgical registries showed that perioperative mortality after iAAA repair varied from <2% to >7%, with the perioperative mortality in the UK being considerably higher than the average (Gibbons C, 2008). This difference in perioperative outcome has also been shown in randomized clinical trials performed in different countries (The UK Small Aneurysm Trial Participants, 1998; Lederle, 2002; Greenhalgh, 2004; Prinssen, 2004). It is difficult to appreciate the reasons for these differences in outcome. As discussed above, higher perioperative mortality is seen in female patients, the elderly and those with increased comorbidities. Patient selection could explain part of this difference in outcome in the national registries (Wanhainen, 2008). However, patient selection should not differ significantly between the above-mentioned randomized clinical trials. The level of centralization varies between countries, and this could be a factor affecting national outcome of AAA repair. As the validity in the national registries varies (Gibbons C, 2008), a closer examination of the reported results is warranted.

# What is the cost of AAA repair?

The human cost of AAA repair in terms of mortality and morbidity has decreased. There is, however, concern that the financial cost of AAA repair has increased excessively due to the introduction of EVAR (Prinssen, 2007).

## Cost of intact AAA repair

It is interesting to put the total cost of AAA repair in perspective to cost of other health care measures. Mean cost of AAA repair in Sweden including 2.5 years of follow-up in the population-based setting was estimated at €28,000 in study II. Table 13 shows cost of treatment of other conditions for comparison. However, comparison of cost of treatment based on different studies as in table 13 is hazardous. Cost of treatment is affected by several factors, such as the costs included in the analysis (e.g. direct and indirect costs), the country and health care system in which the study is performed, and the follow-up period after initial treatment included in the analysis. While bearing these limitations of the comparison below in mind, it indicates that the cost of AAA repair is reasonable when compared to cost of other health interventions.

Table 13. Cost of treatment of different diseases, Euro.

| | Cost | Reference |
|---|---|---|
| Single vessel disease, PTCA (6 months) | 10,340 | (Nagle, 2004) |
| Multivessel disease, PTCA (3 years) | 26,390 | (Nagle, 2004) |
| Multivessel disease, CABG (3 years) | 47,670 | (Nagle, 2004) |
| Treatment of Type II diabetes (3 years) | 9630 | (Martin, 2007) |
| Treatment of lung cancer recurrence (diagnosis to death, median 4.3 months) | 12,518 | (Braud, 2003) |

Follow-up period after diagnosis or operation is presented in parenthesis. PTCA = percutanous transluminal coronary angioplasty; CABG = coronary artery bypass graft. 1 US$ = 0.8 €.

Due to the fatality of AAA rupture and the relatively low risk of treatment, there is no doubt that elective AAA repair can be regarded as cost-effective with a cost per LYG far below the willingness to pay threshold. A rough calculation of the cost-effectiveness of elective AAA repair can be performed with the following assumptions:

Numbers needed to operate (iAAA) to avoid one rupture: 3 (Wilmink, 2003)
Overall mortality due to rupture: 80% (Wanhainen, 2005)
Perioperative mortality iAAA repair: 3% (Wanhainen, 2008)
Mean survival after iAAA repair: 8.9 years (Study I)
Cost of iAAA repair including 10 years follow-up: €34,000 (Study II)

These assumptions result in a cost per LYG of €9000 for iAAA repair compared to non-intervention. Thus, elective repair of an AAA of >5.5 cm is cost-effective, despite the resource-intensiveness of this intervention. The question that remains is which treatment modality that is most cost-effective; or more specifically, if the additional cost of EVAR is justified by the reduction in mortality and morbidity related to this intervention compared to OR.

## Cost of EVAR

Most studies, which compare cost of treatment among AAA patients available for both treatment modalities, have found a higher cost for EVAR compared to OR, table 14. It is also evident from the two randomized trials that cost of EVAR is considerably higher than OR in this setting (EVAR Trial Participants, 2005; Prinssen, 2007). These studies find a much lower cost of AAA repair compared to what was found in the population-based setting in study II.

Table 14. Studies of cost of AAA repair with open and endovascular technique. Cost in Euro.

| Country | Publication year | Cost OR | Cost EVAR | Pre- and postoperative costs included (Yes/No) | Reference |
|---|---|---|---|---|---|
| The Netherlands | 2007 | 13,627 | 18,595 | Yes | (Prinssen, 2007) |
| UK | 2005 | 14,918 | 19,886 | Yes | (EVAR Trial Participants, 2005) |
| Australia | 2005 | 11,298 | 14,112 | Yes | (Hayter, 2005) |
| UK | 2005 | 6404 | 13,154 | No | (Michaels, 2005) |
| USA | 2003 | 7234 | 14,031 | No | (Dryjski, 2003) |
| USA | 2002 | 14,787 | 16,572 | No | (Bosch, 2001) |
| USA | 2000 | 10,037 | 15,988 | No | (Sternbergh, 2000) |
| Australia | 2000 | 10,590 | 16,145 | Yes | (Birch, 2000) |
| USA | 1999 | 10,171 | 10,323 | No | (Seiwert, 1999) |
| USA | 1999 | 12,813 | 16,066 | No | (Patel, 1999) |
| Belgium | 1999 | 9575 | 9048 | No | (Ceelen, 1999) |

1 US$ = 0.8 €, 1 £ = 1.5 €, 1 Australian $ = 0.6 €. Please note that the cost values in the different studies have not been converted to one specific year's money value.

There are several reasons to this difference in outcome between Study II and the previous reports. Firstly, comparison of cost data between studies is cumbersome as differences in included costs are regular and differences in health care system can affect costs and prices (Brox, 2003; Jonk, 2007). As an example, physicians' fees are not always included in cost studies from the US, as this cost is billed separately. Secondly, statistical methodology affects results of cost studies, as discussed in Study III. If outliers are excluded or

median costs are reported, the cost of treatment is presented as lower than the actual mean value for the studied population. Thirdly and most importantly, the population-based nature of Study II results in a somewhat different patient population in this study compared to previous reports. In Study II, all patients from a specific geographical region undergoing iAAA repair were included in the analysis. Thus, the selection bias posed in the randomized clinical trials was not present, presumably resulting in a higher rate of patients with complex aneurysm anatomy (not available to EVAR) and advanced comorbidity (not available to OR). Complex aneurysm anatomy in particular was associated with a higher operative cost in Study II, and could explain the high cost of OR in this study as patients with complex anatomy were selected to OR.

It is important to note that the similar cost of AAA repair with OR and EVAR in Study II does not mean that these two treatment modalities have the same cost for all patients. The randomized trials have shown that cost of OR is lower than EVAR in the average patient eligible for both treatment modalities. It is however possible that cost of EVAR is lower than cost of OR in high-risk patients with appropriate aneurysm morphology (Hynes, 2007).

## Cost-effectiveness of EVAR

Due to the higher cost of EVAR in comparable patients, cost-effectiveness of this technique has been under discussion. The DREAM and EVAR 1 trials both showed a benefit of EVAR compared to OR in terms of perioperative mortality and quality of life. While there was a persistent reduction in aneurysm-related deaths after EVAR compared to OR, the overall mortality was equal for both groups in the long-term (EVAR Trial Participants, 2005). The quality of life of patients who underwent EVAR was inferior to that of OR patients in the long-term, although the difference did not reach statistical significance (EVAR Trial Participants, 2005; Prinssen, 2007). Analysis of the cost-effectiveness of EVAR compared to OR based on these data shows that the ICER of EVAR is above the willingness to pay threshold in most cases, table 15.

Table 15. Incremental cost-effectiveness ratio of AAA treatment with EVAR compared to OR.

| | ΔQALY | ΔCost, Euro | Cost per QALY | Reference |
|---|---|---|---|---|
| **70 years, 5.5 cm** | 0.10 | 17,713 | 165,000 | (Michaels, 2005) |
| **80 years, 6.5 cm** | 1.64 | 21,115 | 12,868 | (Michaels, 2005) |
| **70 years, >5.5 cm** | 0.05 | 9348 | 187,836 | (Blackhouse, 2008) |
| **70 years, 6.0 cm** | -0.01 | 4300 | OR dominant | (Prinssen, 2007) |

1 £ = 1.5 €; 1 Canadian $ = 0.7 €.

Despite this, an appraisal of the cost-effectiveness of EVAR performed by the National Institute for Health and Clinical Excellence (NICE) in the UK recently found health-economic support for further use of EVAR for iAAA repair in the UK (NICE, 2009). Interestingly, in the initial base-case analysis the NICE appraisal only found EVAR cost-effective in elderly patients (>75 years of age) with moderate to poor fitness for operative repair. This was an analysis based on data from the current literature, and EVAR was not cost-effective for the average AAA patient in this scenario. Additional analyses were performed after consultation of clinical experts. In the additional analyses, it was assumed that several of the variables affecting cost-effectiveness of EVAR have changed since the published randomized trials were performed. Based on clinical expert input, the long-term aneurysm related mortality after EVAR and the re-intervention rates were decreased compared to data from the EVAR 1 trial. Additionally, it was assumed that the long-term follow-up cost after EVAR has decreased, due to changes in follow-up practice with duplex instead of CT and decreased rate of re-intervention e.g. for type II endoleaks. Indeed, recent reports support these assumptions, as the follow-up and re-interventions after EVAR have changed with a decrease in cost as a consequence (Steinmetz, 2004; Black, 2009; Dias, 2009). Based on these assumptions, EVAR was cost-effective for the overall average AAA patient, with an ICER of €18,000 per QALY. In a subgroup analysis, ICER for EVAR was €13,500 per QALY for patients with moderate and poor fitness, and €106,500 per QALY for patients with good fitness. Thus, OR is still the most cost-effective treatment for the young and relatively healthy patients with AAA. Together with the insufficient long-term follow-up data on EVAR this could motivate a continuous important role for OR among patients with AAA detected through screening. The final recommendation of the NICE appraisal was to support use of EVAR preferably at high-volume centers and to leave the decision of operative technique for iAAA repair to be taken in consensus between the patient and the clinician.

# What selection criteria are appropriate for AAA screening?

## Prevalence of AAA at screening

The overall prevalence of AAA in the Multicentre Aneurysm Screening Study (65-74 years old males) was 5%, and 4% in the Viborg trial (64-73 years old males) (Ashton, 2002; Lindholt, 2005). Higher prevalence of the disease has been reported in specific subgroups of patients. In a cohort of 139 patients operated on for popliteal artery aneurysm and no previous AAA, 24.5% developed an AAA over a mean follow-up of 7 years (Ravn, 2008). A high prevalence of disease has also been shown among first-degree

relatives to patients with AAA as well as in smokers and patients with atherosclerotic vascular disease, table 16. Studies of AAA prevalence among women are, however, scarce. In a report by Derubertis et al where women with cardiovascular risk factors or family history of AAA were invited to screening, the overall prevalence of AAA was 0.7% (mean age 70 years), table 16. The prevalence of the disease increased to >6% if several risk factors were present (Derubertis, 2007).

Table 16. Prevalence of AAA in different subgroups of patients.

| | Prevalence of AAA | Reference |
|---|---|---|
| Siblings to patients operated for AAA | 29% | (Bengtsson, 1989) |
| Children to patients with fatal AAA | 20% | (Bengtsson, 1992) |
| Patients with intermittent claudication | 15% | (Bengtsson, 1989) |
| Patients with carotid artery stenosis | 11-18% | (Carty, 1993; Kang, 1999) |
| White male smokers | 5.9% | (Lederle, 1997) |
| Women 65-74 years | 0.6% | (Derubertis, 2007) |
| Women with previous tobacco use | 1.0% | (Derubertis, 2007) |
| Women with heart disease | 2.0% | (Derubertis, 2007) |
| Women >65 years of age, with history of tobacco use, heart disease and positive family history | 6.4% | (Derubertis, 2007) |

The overall prevalence of AAA in Study IV was 3.1%. While this might seem as a relatively low prevalence in a high-risk population, it is important to note that 45% of the screened population was female, the mean age was lower than in the previously discussed studies (66.5 years) and only 38% of the patients had a duplex-verified arterial stenosis verifying manifest atherosclerotic disease. The prevalence of AAA was 6.5% among men with duplex verified arterial stenosis and 2.9% among men without stenosis. The corresponding figures for women were 2.7% and 0.8%.

## Cost-effectiveness of screening

Screening for AAA among the elderly male population is cost-effective, according to several randomized studies, table 17 (Wilmink, 2003; Lindholt, 2006; Thompson, 2009). The ICER for AAA screening ranged between €886 and €11,400 per LYG in various studies, table 17. It was therefore consistently below the usual willingness to pay threshold and compared favorably with the cost-effectiveness of several other health-care measures, table 18.

As previously mentioned, general screening of the elderly male population is being implemented in several countries (Wanhainen, 2006; Scott, 2008; Swedish Council on Technology Assessment in Health Care, 2008). In light of this development, question remains regarding the role of selective screening of specific patient populations.

Table 17. Incremental cost-effectiveness ratio of screening for AAA in the elderly male population according to previous studies.

| | Cost, Euro | Clinical outcome measure | Reference |
|---|---|---|---|
| *Randomized trials* | | | |
| 65-74 years old male population | 11,400 | LYG | (Thompson, 2009) |
| 64-73 years old male population | 9507 | LYG | (Lindholt, 2006) |
| Men >50 years | 886 | LYG | (Wilmink, 2003) |
| *Health-economic models* | | | |
| 65-year old men | 4336 | QALY | (Montreuil, 2008) |
| 65-year old men | 7760 | LYG | (Henriksson, 2005) |
| 65-year old men | 8379 | LYG | (Wanhainen, 2005) |
| 70-year old men | 11,267 | LYG | (Wanhainen, 2005) |
| 70-year old men | 8972 | QALY | (Lee, 2002) |

1 £ = 1.5 €; 1 Canadian $ = 0.7 €; 1 US$ = 0.8 €.

Screening of patients with heredity for AAA and history of popliteal artery aneurysm is regarded as uncontroversial, and should not be affected by the introduction of general screening programs. The disease develops earlier in these subgroups and the prevalence of AAA can be high already at age <65 (Bengtsson, 1989; Bengtsson, 1992; Ravn, 2008). Therefore screening in these populations is often offered at a younger age than the 65-years limit that is common for general population screening. Screening in these high-risk populations is bound to be cost-effective, considering the long expected survival in patients who are detected with AAA at a relatively young age. In a Markov model based analysis, a cost-effectiveness ratio of €6400 per LYG was estimated for 65-year old patients with popliteal artery aneurysm and €7000 per LYG for siblings to AAA patients (Wanhainen, 2005).

When it comes to screening among patients with suspected atherosclerotic disease (as described in studies IV and V), a general screening program would probably decrease the prevalence of previously unknown AAA in this population. However, general screening of the male population at age 65 would not affect the detection rate of AAAs in male patients below 65 or female patients. Furthermore, there is still an uncertainty on the long-term risk of developing an AAA after a negative scan. As previously described, the prevalence of AAA in the male patients at the vascular laboratory <65 years of age varied from 1.4 to 3.8% depending on presence of duplex verified arterial stenosis. No AAA was detected in women <65 without duplex-verified arterial stenosis. In other female patient groups, the prevalence of AAA varied between 1.4 and 3.0%. The Markov model analysis showed that screening was cost-effective despite a low prevalence in these patient groups. Furthermore, screening among patients at the vascular laboratory does not add any administrative burden on the laboratory. Thus it seems reasonable to continue with screening in this setting. However, it would be appropriate to improve patient information regarding this screening. Current

practice at our institution is to perform the screening as clinical routine without specific patient information. Considering the rate of patients who are not further followed-up despite detection of AAA and the lack of knowledge on the potential negative effects of diagnosis on quality of life of patients, it would be appropriate to define inclusion and exclusion criteria.

Table 18. Cost-effectiveness of different health care interventions.

| | **Cost, Euro** | **Clinical outcome measure** | **Reference** |
|---|---|---|---|
| Influenza immunization in the elderly | -* | NA | (Nichol, 1998) |
| Betablocker post myocardial infarction | 4800 | QALY | (Weinstein, 1985) |
| Coronary bypass, angina and three vessel disease | 5040 | QALY | (Weinstein, 1985) |
| Kidney transplantation | 8000 | LYG | (Winkelmayer, 2002) |
| Breast cancer screening | 12,800 | LYG | (Lindfors, 1995) |
| Colorectal screening, biennial faecal-occult-blood test | 30,000 | Prevented death | (Swedish Council on Technology Assessment in Health Care, 2002) |
| Medical treatment of hypertension | 20,000 | QALY | (Weinstein, 1985) |
| Treatment of end-stage renal disease with hospital based dialysis | 44,000 | LYG | (Winkelmayer, 2002) |
| Prostate cancer screening, 60-69 year old | 52,727 | LYG | (Coley, 1997) |

* Immunization for influenza among the elderly is the dominant strategy and renders positive utility and a cost saving of €58 per vaccinated individual. 1 US$ = 0.8 €. 1 Swedish Krona = 0.1 €.

# Conclusions

The long-term survival after AAA repair was somewhat lower than that of the general Swedish population. The 5-year relative long-term survival was 90% after iAAA repair, and 87% after rAAA repair.

Over the last two decades, the long-term survival improved after iAAA repair and was stable after rAAA repair. Changes in patient demography and case-mix towards older patients, higher proportion of patients with comorbidities and an increasing use of EVAR have thus not had any negative effects on long-term outcome after operation.

The total cost of elective AAA repair was similar for OR and EVAR in a non-randomized population-based setting, with a mean cost of €28,193 including 2.5 years of follow-up.

Patients operated on electively for AAA and selected for OR had anatomically complex aneurysms more often, with ICU care as the major cost-driver. Patients selected for EVAR were older and had more serious co-morbidities, with stentgrafts as the major cost-driver.

There is currently a lack of consistency in methods used for analysis of cost data in vascular surgery. An understanding of the specific qualities of cost data, and the economic perspective in which these data are used is of importance.

The results of health economic reports on cost of treatment modalities can be highly dependent on how data are presented, and on the statistical methodology used. A high degree of openness when presenting cost data in medical reports is desirable in order to avoid misleading conclusions.

In a selective high-risk screening program, among patients referred for arterial examination at the vascular laboratory, the total prevalence of AAA was 3%, with higher prevalence among male patients, those with atherosclerotic disease and the elderly.

Among all men above 60-years of age and among women above 65-years of age with a duplex-verified arterial stenosis, the prevalence of AAA was ≥3%, justifying screening in these groups, from a prevalence point of view.

Patients with AAA detected in selective screening at the vascular laboratory had a high level of morbidity and inferior long-term survival compared to the general population. Elective AAA repair rate was lower in this group compared to patients with AAA detected in general screening programs.

Selective screening for AAA among patients referred to the vascular laboratory for suspected arterial disease was cost-effective under most assumptions with an estimated ICER at base-case of €11,084 per LYG compared to non-screening.

# Future perspectives

The treatment of AAA has developed significantly over the past 20 years with the introduction of EVAR (Volodos, 1986; Parodi, 1991; Volodos, 1991), the timing of intervention established by randomized trials (The UK Small Aneurysm Trial Participants, 1998; Lederle, 2002), improved postoperative care (Papia, 2006; Laukontaus, 2007), and the introduction of population-based screening for AAA (Wanhainen, 2006; Scott, 2008). Thanks to these developments, more patients with AAA can be treated, more patients survive AAA repair and more ruptures are avoided. There are several areas were further epidemiological research can guide improvements in the care of the AAA patient. Some of these areas are discussed below.

## AAA repair

In the perspective of increasing EVAR volumes and decreasing volumes of OR (often with challenging anatomy), the issue of volume-outcome relationship would merit further evaluation. The Swedvasc database offers an exceptional opportunity to study the relationship of volume and outcome on a national level in Sweden. The national differences in outcome after AAA repair could be further explored, with an ambition to identify success factors and risk factors affecting outcome. Improvements in outcome of care of female patients would be desirable, as the current results seem to be affected by gender. With the introduction of new devices for endovascular treatment of AAA and changes in follow-up and re-interventions after EVAR, continued evaluation of the health economic value of this technique can be of interest, both for iAAA and rAAA repair.

## Screening for AAA

Screening is being widely implemented in several countries. If detection of an AAA at screening would have a negative effect on quality of life, the benefits of screening would be largely outweighed by the costs. It would therefore be of interest to measure quality of life among screening patients in the long term to identify the potential effect of screening on this aspect. Screening results in detection of many small aneurysms among patients with

latent cardiovascular disease. Questions still remain regarding the best possible screening strategy. Some areas for further research include the definition of an optimal age for screening, the potential need for repeat screening after 5-10 years, and evaluation of screening for women. The possible effects of general health interventions to avoid future cardiovascular events in the population with small aneurysms would also merit further studies. For example, smoking is an important risk factor for development and growth of AAA as well as cardiovascular and pulmonary disease in general. The effect of an intensive smoke cessation program on AAA-related and cardiovascular morbidity and mortality in the screening population could be studied.

# Populärvetenskaplig sammanfattning (Summary in Swedish)

Abdominellt aortaaneurysm (AAA) innebär en sjuklig vidgning av stora kroppspulsådern i buken. Sjukdomen är vanligare hos män och förekomsten ökar med åldern. Naturalförloppet för bråcket (aneurysmet) är att tillväxa och så småningom brista (rupturera). Totalt i befolkningen orsakar ruptur erat AAA 700-1000 dödsfall per år i Sverige

För att förhindra ruptur rekommenderas en förebyggande operation där bråcket ersätts av en konstgjord åder. Detta sker antingen med en öppen operation via buken eller med en minimalinvasiv (endovaskulär) operation via ljumskarna. I och med införandet av endovaskulära tekniker och en förbättrad vård före och efter operation kan allt äldre och sjukare patienter erbjudas operation. Operation kan också göras akut när aneurysmet har brustit. De flesta patienter med ruptur dör dock innan de hinner till sjukhus. Akuta operationer är vidare mycket resurskrävande och har hög dödlighet. Med hjälp av resultat från riskfaktor studier kan lämpliga målgrupper för screening identifieras.

I denna doktorsavhandling studerades olika epidemiologiska och hälsoekonomiska aspekter av AAA. I **delarbete I** analyserades långtidsöverlevnaden efter behandling av aortaaneurysm i Sverige bland 12834 patienter från det svenska kärlregistret Swedvasc. För patienter som överstod operation för intakt AAA var den relativa 5-års överlevnaden 90% av överlevnaden hos en normal svensk befolkning av samma ålder och kön. Efter operation för rupturerad AAA var den relativa 5-års överlevnaden för patienter som överstod ingreppet 87%. Långtidsöverlevnaden efter intakt AAA operation ökade med tiden, trots att andelen äldre patienter med generell hjärt- och kärlsjuklighet ökade på senare år. Långtidsöverlevnaden efter operation för rupturerat AAA var oförändrad över tid.

I **delarbete II** analyserades kostnaden för planerad behandling av AAA för samtliga patienter från Uppsala län opererade vid Akademiska sjukhuset 2001-2005 (109 patienter, 58 öppna och 51 endovaskulära operationer). Kostnaden för operation inklusive 2,5 års uppföljning var 28193 Euro (motsvarande ca 254000 kronor). Det fanns skillnader i kostnadsstruktur mellan behandlingsmetoderna, men totalkostnaden var lika. Patienter som opererades med öppen teknik hade anatomiskt mer komplexa aneurysm, och intensivvård stod för den största andelen av kostnaden i denna grupp. Patienter

som selekterades till endovaskulär operation var äldre och sjukare, och kostnaden för stentgrafter var den största posten i denna grupp.

En litteraturgenomgång som genomfördes i **delarbete III** visade att flera olika statistiska metoder användes i befintliga artiklar vid jämförelse av kostnader för behandling av AAA med öppen och endovaskulär teknik. De vanligaste statistiska metoderna för jämförelse av kostnader var t-test, Mann-Whitney U-test, logaritmisk transformation och bootstrap teknik. Applicering av dessa olika metoder på kostnadsdata från studie II visade att tolkning av resultaten till stor del berodde på vilken statistisk metod som användes. Studien visar på behovet av försiktighet vid tolkning av kostnadsstudier.

I **delarbete IV** studerades förekomsten av AAA och faktorer associerade med AAA bland ca 6000 patienter som undersökts för aneurysm i samband med ultraljudsundersökning av kärlen på ett kärllaboratorium. Man fann en total förekomst av AAA på 3%. Förekomsten av AAA var associerad med manligt kön, hög ålder och förekomst av ultraljudsverifierad förträngning i artärer. Förträngning i benartärer hade högst association med förekomst av aneurysm. Bland alla män >60 år samt bland kvinnor >65 år med ultraljudsverifierad kärlförträngning var förekomsten av AAA tillräckligt hög för att potentiellt motivera screening.

I **delarbete V** genomfördes en långtidsuppföljning av 181 patienter som identifierats i studie IV med AAA upptäckt vid screening på ett kärllaboratorium. Planerad operation för AAA genomfördes hos 22% av patienterna. På 5-års sikt var dödligheten två gånger högre hos AAA patienter än den för en matchad normalbefolkning. En hälsoekonomisk analys baserad på insamlade data visade att screening trots det var kostnadseffektiv, med en kostnad per sparad levnadsår på 11084 Euro (motsvarande ca 100000 kronor), vilket är långt under accepterat tröskelvärde på ca 50000 Euro (ca 450000 kronor).

Sammanfattningsvis har överlevnaden efter planerad operation för AAA förbättrats med tiden, trots att andelen äldre patienter med övrig sjuklighet har ökat. Kostnadsstrukturen för behandling av AAA med öppen och endovaskulär teknik skiljde sig åt, och totalkostnaden inklusive 2,5 års uppföljning var 28000 Euro per patient. Resultaten av kostnadsstudier berodde dock till stor del på de patienter som inkluderades i studien och statistiska metoder som användes vid analys av data. Förekomsten av AAA var 3% hos patienter som remitterats till kärllaboratoriet för artärundersökning. Screening för AAA bland dessa patienter var kostnadseffektivt.

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