Abdominal aortic aneurysm

– Aspects on diagnosis and treatment

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Medicine is a science of uncertainty and an art of probability.

Sir William Osler

To Valdemar, Lilly, Alice, Signe, and Lisa

Abstract

Background

An abdominal aortic aneurysm (AAA) is an abnormal widening of the aorta with a risk of rupture if it grows to a large diameter. Rupture is associated with massive bleeding and a poor prognosis for survival.

Aims

The aim of this thesis was to evaluate the results of surgical intervention in patients with AAAs detected by population-based screening, including comparisons with the results in patients with aneurysms that were not detected by screening. A further aim was to investigate how common misdiagnosis is in the emergency department in patients seeking care for a ruptured AAA (rAAA), and how misdiagnosis affects the prognosis. A third aim was to investigate whether it is beneficial to treat patients with a primary open abdomen with delayed closure after open repair for rAAA.

Methods

Patients with AAA were identified in the Swedish Vascular Registry (**Studies 1–4**) and the Swedish Cause of Death Registry (**Study 4**). Additional information was obtained through review of medical charts (**Studies 2–4**). In **Study 1**, mortality, complications, and method of surgical intervention were compared in patients with AAAs detected by screening and in age-matched controls with AAAs that were not detected by screening. In **Study 2** and **Study 4**, the outcome in patients with a ruptured abdominal aortic aneurysm (rAAA) who were misdiagnosed at the first assessment in the emergency department was compared to the outcome in patients who were correctly diagnosed initially. **Study 2** included patients who reached surgery and **Study 4** included all patients with rAAA, whether or not they reached surgery. In **Study 3**, mortality

and complications in patients treated with a primary open abdomen after open repair for rAAA were compared to a propensity score-matched control group in which the majority of patients had the abdomen closed at the end of the procedure.

Results

Study 1: A higher proportion of the screening-detected patients were treated with open repair (56% vs. 45% in those with AAAs not detected by screening). The mortality 30 days, 90 days, and 1 year after open repair was similar in patients with screening detected and non screening-detected aneurysms. Mortality at 30 days and 1 year after Endovascular Aortic Repair (EVAR) was similar in both groups. Mortality at 90 days after EVAR was lower in the screening-detected compared to the non screening-detected patients (0% vs. 3.1%; $p = 0.04$). The overall 30-day mortality (including patients treated with either open repair or EVAR) was 0.6% in screening-detected patients and 1.4% in non screening-detected patients. ($p = 0.45$). The adjusted odds ratio for the primary endpoint (mortality or major complication at 30 days) was 1.64 (95% CI 0.82–3.25) in non screening-detected patients.

Studies 2 and 4: Misdiagnosis was common and occurred in more than one-third of the patients with rAAA. Overall, the mortality was 74.6% in misdiagnosed patients and 62.9% in correctly diagnosed patients ($p = 0.01$). The adjusted odds ratio for mortality in the whole cohort of misdiagnosed patients was 1.83 (1.13–2.96). In patients who reached surgery, there was no significant difference in mortality between misdiagnosed patients and correctly diagnosed patients.

Study 3: There were no significant differences in mortality or major complications between patients treated with a primary open abdomen with delayed closure and patients treated with primary closure of the abdomen.

Conclusion

The contemporary mortality after AAA surgery in Sweden was low irrespective of whether or not screening was used for detection. Patients with AAAs detected by screening had the same comorbidities and outcome as those with non screening-detected aneurysms, except for 90-day mortality after EVAR, which was lower in the screening group.

Misdiagnosis is common in patients who seek care for a rAAA, and misdiagnosis is associated with a substantially higher risk of dying from the ruptured aneurysm.

No survival advantage and no lower frequency of complications was observed in patients treated with a primary open abdomen and delayed closure after open repair for rAAA as compared to a propensity score-matched control group where the majority of patients were treated with primary closure of the abdomen.

Sammanfattning på svenska

Bukaortaaneurysm (även benämnt Abdominellt Aorta Aneurysm eller AAA) innebär att den del av kroppspulsådern (aorta) som är belägen i buken har utvidgat sig på ett onormalt sätt. Sjukdomen är förhållandevis vanlig och förekommer hos omkring 1,5 % av Sveriges 65-åriga män. Hos kvinnor är bukaortaaneurysm betydligt mer sällan förekommande. Den principiella faran med ett bukaortaaneurysm är att det finns en risk för att det brister. Denna risk är mycket låg om aneurysmet är litet, men ju större aneurysmet är, desto större blir risken att det brister. Ett brustet bukaortaaneurysm är ett mycket allvarligt tillstånd förenat med massiv blödning. Majoriteten av de människor som drabbas av ett brustet bukaortaaneurysm överlever inte, men det finns en chans att överleva vid snabb kirurgisk behandling. Dödligheten är tyvärr hög även hos patienter som snabbt kommer till kirurgisk behandling, men utan sådan är det inte möjligt att överleva ett brustet bukaortaaneurysm. Vid upptäckt av ett större bukaortaaneurysm innan det brister kan det finnas möjlighet till kirurgisk behandling med en låg dödlighet. Därav är det en klar fördel att diagnosticera ett bukaortaaneurysm innan de brister. Screening av 65-åriga män med ultraljud erbjuds i hela Sverige. Syftet med screeningen är att påvisa bukaortaaneurysm och ge möjlighet till planerad behandling om aneurysmet är eller blir så stort att risken för att det brister är hög.

I denna avhandling studeras sjukdomen bukaortaaneurysm ur tre olika synvinklar. I **Studie 1** utvärderas resultatet av kirurgisk behandling hos patienter där man funnit ett bukaortaaneurysm i samband med screening. Resultaten hos denna patientgrupp jämförs med resultatet hos de patienter där man funnit ett bukaortaaneurysm på något annat sätt än inom ramen för screening programmet. Studien visar att dödligheten efter kirurgisk behandling är låg hos såväl patienter med bukaortaaneurysm som upptäckts vid screening som hos patienter med bukaortaaneurysm som upptäckts på andra sätt. Mortaliteten var lägre 90 dagar efter operationen hos patienter med screeningupptäckta aneurysm, i övrigt påvisades inga avgörande skillnader i resultatet efter kirurgisk behandling

mellan de två grupperna.

I **Studie 2 och 4** undersöks hur ofta patienter som insjuknat med ett brustet bukaortaaneurysm blir felbedömda på akutmottagningen och hur detta påverkar möjligheterna att överleva. Det undersöks även hur en initial felbedömning på akutmottagningen påverkar förekomsten av allvarliga komplikationer hos de patienter som når kirurgisk behandling. I båda studierna så blev mer än en tredjedel av patienterna felbedömda i samband med den första undersökningen av läkare på akutmottagningen. Patienter som blev felbedömda löpte en avsevärt större risk att dö än patienter där man misstänkte eller säkerställde brustet bukaortaaneurysm redan vid den första undersökningen. Hos patienter där man efter en första felbedömning sedermera i akutskedet kunde konstatera ett brustet bukaortaaneurysm, och behandla tillståndet kirurgiskt, hade inte sämre chanser att överleva än patienter som fick rätt diagnos direkt.

I **Studie 3** undersöks huruvida det är gynnsamt att lämna buken öppen med ett specialanpassat vakuumförband, och sluta buken i ett något senare skede, hos patienter som opererats med öppen teknik för ett brustet bukaortaaneurysm. Skälet till att göra detta skulle vara att undvika att ett högt tryck utvecklas i bukhålan efter operationen till följd av blödningen och svullnad av organ och vävnad i bukhålan. Det är känt att om trycket i bukhålan blir påtagligt högt så påverkas viktiga kroppsfunktioner såsom blodcirkulation, andning och njurfunktion, och möjligheten att överleva och återhämta sig försämras. Patienter som behandlats med öppen buk i initialskedet efter en öppen operation för brustet bukaortaaneurysm jämfördes med en patientgrupp där man i flertalet av fallen hade stängt buken vid operationens slut. Studien kunde inte påvisa någon skillnad i dödlighet eller förekomst av allvarliga komplikationer mellan patienter som behandlats med öppen buk initialt och kontrollgruppen.

Sammanfattningsvis så konstaterades i denna avhandling att mortaliteten är låg vid planerad kirurgisk behandling av bukaortaaneurysm i Sverige idag. Resultaten 30 dagar efter operationen var likvärdiga hos patienter med screeningupptäckta och icke screeningupptäckta aneurysm.

Det konstaterades även att det är vanligt förekommande att patienter som söker vård för ett brustet bukaortaaneurysm blir felbedömda på akutmottagningen och att detta är förenat med en klart ökad risk att inte överleva.

Ingen fördel med att behandla patienter som opererats med öppen teknik för ett brustet bukaortaaneurysm med öppen buk i initialskedet efter operationen kunde påvisas, när sådan behandling jämfördes med en patientgrupp där man slutit buken vid operationens slut i merparten av fallen.

List of papers

This thesis is based on the following studies, referred to in the text by their number.

1. Linné A., Smidfelt, K., Langenskiöld, M., Hultgren, R., Nordanstig, J., Kragsterman, B., Lindström, D. **Low Post-operative Mortality after Surgery on Patients with Screening-detected Abdominal Aortic Aneurysms: A Swedvasc Registry Study** Eur J Vasc Endovasc Surg (2014) 48, 649-656.
2. Smidfelt, K., Drott, C., Törngren, K., Nordanstig J, Herlitz, J., Langenskiöld M. **The Impact of Initial Misdiagnosis of Ruptured Abdominal Aortic Aneurysms on Lead Times, Complication Rate, and Survival** Eur J Vasc Endovasc Surg (2017) 54, 21-27
3. Smidfelt, K., Nordanstig, J., Wingren, U., Bergström, G., Langenskiöld, M. **Primarily open abdomen compared to primary closure of the abdomen after open repair for ruptured abdominal aortic aneurysms: a study of mortality and complications.** Submitted
4. Smidfelt, K., Nordanstig, J., Davidsson, A., Törngren, K., Langenskiöld, M. **Misdiagnosis of ruptured abdominal aortic aneurysms is common and associated with increased mortality.** Submitted

Content

Abbreviations

AAA	Abdominal Aortic Aneurysm
ACS	Abdominal Compartment Syndrome
APP	Abdominal Perfusion Pressure
CI	Confidence Interval
CT	Computed Tomography
ED	Emergency Department
EVAR	Endovascular Aortic Repair
iAAA	intact Abdominal Aortic Aneurysm
IAH	Intraabdominal Hypertension
IAP	Intraabdominal Pressure
ICU	Intensive Care Unit
IQR	Interquartile Range
MAP	Mean Arterial Pressure
MASS	Multicentre Aneurysm Screening Study
MR	Magnetic Resonance Tomography
OR	Open Repair
rAAA	ruptured Abdominal Aortic Aneurysm
RCT	Randomized Controlled Trial
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
Swedvasc	The Swedish National Registry for Vascular Surgery
UK	United Kingdom
WSACS	World Society of the Abdominal Compartment Syndrome

Introduction and background

Abdominal aortic aneurysms

An aneurysm is a localized widening of an artery or vein. Thus, an abdominal aortic aneurysm (AAA) is a localized abnormal widening of the abdominal aorta. The aorta is the largest artery of the human body.

AAAs with large diameters have a risk of rupture, a dramatic event accompanied by massive bleeding and a poor prognosis for survival.

The ultimate goal of research on AAA is to reduce the risk of dying from a ruptured AAA (rAAA).

This thesis focus on three different steps in the chain of care of individuals with AAAs: (1) screening in order to find AAAs before rupture, (2) the assessment of patients with rAAA who seek care in an emergency department (ED), and (3) whether it is beneficial to treat patients operated with open surgical repair of an AAA with an open abdomen regimen initially after the procedure.

Definition

The term aneurysm originates from an ancient Greek word meaning dilatation. An aortic aneurysm is a dilatation of the aorta including all layers in the vessel wall (intima, media, and adventitia). There are various definitions of AAA. The most common and generally used definition is the one proposed by McGregor in 1975, that an aneurysm is an infrarenal aortic diameter of 30 mm or larger[1]. This definition is based on previous work by Steinberg and Stein, who reported 200 cases of

abdominal aortic aneurysm diagnosed by aortography[2] and work by Leopold et al, who reported on ultrasonic abdominal aortography in 1970[3]. Another definition of AAA is that it is a ratio between the diameter of the infrarenal and suprarenal aorta > 1.5[4,5]. The lack of a uniform definition of AAA is a weakness of epidemiological studies on AAA. It has been demonstrated that varying definitions of rAAA influence the reported prevalence of the disease[6].

Abdominal aortic aneurysms are located between the diaphragm and the aortic bifurcation. A weakening of the aortic wall causes dilatation of the aorta. The most common location of an aortic aneurysm is below the renal arteries (infrarenal aneurysm)[7]. Juxtarenal aneurysms begin immediately below the renal arteries, pararenal aneurysms involve the renal arteries, and suprarenal aneurysms involve one or more visceral arteries. AAAs can be treated surgically by either open repair (OR) or endovascular aortic repair (EVAR). The more cranially an AAA is located, the more demanding is the surgical or endovascular repair.

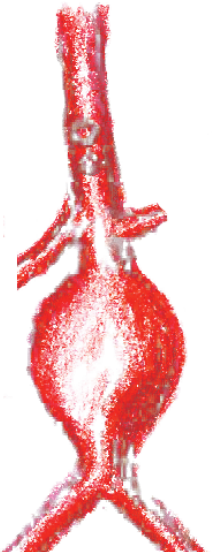

Illustration 1 Abdominal aortic aneurysm located below the renal arteries, i.e. an infrarenal aneurysm.

The natural course of an aneurysm is generally a progressive expansion over a number of years, but the growth rate can vary considerably between individuals. The diameter of a normal abdominal aorta has been reported to be 16.8 ± 2.9 mm in men over 50 years and 14.6 ± 1.9 mm in women of the same age[8]. However, the diameter of the aorta varies according to age, sex, and body surface area, and population-based normative values are available[9].

Historical aspects

The first written evidence of aneurysms has been found in the Ebers papyri from ancient Egypt, dating back to 1550 BC [10]. Aneurysms were also described as "Sira Granthi" or tumour of blood vessels in the Indian medical text Suhruta Samhita, around 600–800 BC[11]. Various attempts to treat abdominal aortic aneurysms have been made historically, including attempts to ligate the aneurysm, which was practised by the Greek surgeon Antyllus as early as 126–216 AD [12]. Ligation continued to be an option for surgical treatment of aneurysmal disease and was reported in 1817, when Mr Cooper ligated the aorta on a young man with an iliac aneurysm, who died shortly after the procedure[13].

A successful attempt to ligate an aneurysm was reported by Dr Matas in 1923, when a syphilitic aortoiliac aneurysm in a 22-year-old woman was ligated. Despite several surgical complications, she survived the procedure and died from a haemorrhage from a bleeding pulmonary tubercular cavity 17 months after the procedure[14].

Other—mostly fatal—attempts to treat AAAs were also reported in the middle of the twentieth century, including methods of inducing thrombosis of the aneurysm by introducing thin wires through which the blood in the aneurysm was heated to 80°C [15].

Wrapping of AAAs in cellophane has been tried, to induce fibrosis and reduce expansion and the risk of rupture. Albert Einstein was treated with this method in 1948. His aneurysm ruptured 6 years later and he then refused any further surgical attempts[16]. Attempts to restore a tubular lumen by arteriorraphy have also been reported[17].

A major drawback of ligation of the aorta or deliberate induction of thrombosis of an aortic aneurysm is naturally the risk of severe ischaemia of the lower parts of the body that is accompanied by such a procedure. In 1951, Freeman et al. reported the first successful procedures for abdominal aortic aneurysms, in which the blood flow through the aorta

was preserved by using an autologous vein (the iliac vein or internal jugular vein)[18]. In 1951–1952, Dubost described AAA resection with preservation of blood flow by using a preserved human arterial graft[19]. A couple of years later (1954), Schumacker et al. reported on the use of artificial grafts for bypass in the treatment of AAAs[20], a method that has been used in numerous patients since then, and still is.

The Ukrainian surgeon Nicholas Volodos contributed a major step in vascular surgery by reporting on endovascular treatment of AAAs in 1986[21]. However, it was a later publication in English by Juan Carlos Parodi in 1991 that was responsible for the introduction of EVAR throughout the world[22].

Pathophysiology

The pathophysiological basis of AAA formation is complex and multifactorial. It was previously believed that aneurysm formation was a manifestation of atherosclerosis. It is now known that the pathophysiology of AAA formation involves a degenerative process involving the arterial wall. It has been suggested that localized haemodynamic stress, fragmented proteins in the tunica media, genetic predisposition, and unknown factors lead to attraction of inflammatory cells to the arterial wall. Chemokines, cytokines, and reactive oxygen species are released—with a resulting further influx of leukocytes and activation of proteases, including matrix metalloproteases (MMPs). This results in degradation and remodelling of the aortic wall, further dilatation, and aneurysm formation[23].

It is known that aneurysms of the common and internal iliac artery may occur simultaneously with AAAs[24]. However, aneurysms of the external iliac arteries are very rare[25], suggesting that embryological factors may also play a role in the pathogenesis of aneurysms[26].

Epidemiology

The prevalence of abdominal aortic aneurysms has declined in recent years in many parts of the world, but not all. Western Europe, North America, and Australasia have had the most pronounced decline, while Oceania, tropical Latin America, sub-Saharan Africa, and Central Asia showed an increase in the prevalence of AAA between 1990 and 2010[27]. The prevalence of AAA was reported to be 2.2% in 65-year-old men in Sweden in 2011[28], as compared to 3.5–5.7% in men < 70 years of age in earlier reports from screening studies performed in the United Kingdom, Denmark, and Australia [29]. The Swedish prevalence was even lower in a report by Wanhainen et al. from 2016, with a prevalence of AAA of 1.5% in 65-year-old men[30].

It has been proposed that the declining incidence can be explained by declining smoking in the population[28,31-33]. AAA is around 4–6 times more common in men than in women[34-36]. In a Swedish study from 2013, the prevalence of AAA in 70-year-old women was 0.5%[37].

Despite the declining prevalence of the disease in some parts of the world, ruptured abdominal aortic aneurysms (rAAAs) have an estimated global annual mortality rate of 150,000 individuals[38].

Risk factors

Several risk factors associated with the development of AAA, expansion, and rupture have been studied, including age, sex, a family history, smoking, hypertension, diabetes mellitus, obesity, hyperlipidaemia, alcohol consumption, and physical activity.

Age

AAA is predominantly a disease of the elderly; it is uncommon in younger people. Advancing age is a risk factor that has been reported in several studies[39-43]. A large study in the United States, including 3.6 million self-referred individuals who paid for vascular screening, examined the prevalence of AAA at different ages. The cohort studied consisted of 64% women and 36% men. The prevalence of AAA in asymptomatic individuals was 0.05% in subjects aged 40–50 years, 0.22% in those aged 51–60 years, 0.84% in those aged 61–70 years, 1.73% at 71–80 years, 2.55% at 81–90 years and 3.35% at 91–100 years[44]. The authors did not report gender-specific prevalence.

Sex

Male gender is a risk factor for AAA. The prevalence of AAA in men is 4–6 times greater than that in women[34-37,39-43]

The reason for the higher prevalence of AAAs in men is poorly understood. The possibility of genetic predisposition in men is obvious, but environmental factors such as smoking habits probably also contribute to the difference in prevalence. Mouse models have indicated that androgens have a role in the development of AAAs [45,46]. Animal models in recent publications have also indicated that the androgen receptor may have an important role in aneurysm formation[47,48].

Smoking

Smoking is the strongest risk factor for AAA[34,36,39-43,49] (OR > 3.0 in all studies). The association between smoking and AAA is stronger than between smoking and other forms of cardiovascular disease[50]. Only lung cancer and chronic obstructive pulmonary disease have a stronger epidemiological association with smoking than AAA [51].

The association between smoking and AAA has been reported to increase

significantly with the number of years of smoking and to decrease significantly with the number of years after stopping smoking[41]. Smoking is also associated with an increased expansion rate[52,53].

Family history

A family history is a known risk factor for AAA. In a Swedish study, the risk of developing AAA was approximately twice as much in individuals with a first-degree relative who has been diagnosed with AAA (compared to individuals with no family history)[54]. In a meta-analysis, first-degree relatives of patients with AAA were also found to be significantly more affected by AAA, indicating that the disease has a genetic basis[55]. However, the genetic background of the disease has not been studied completely, and many questions on the genetics of AAA remain to be answered.

Other risk factors

Hypertension, hypercholesterolaemia, other vascular disease, and greater height have also been suggested to be risk factors for the development of AAA, but with less solid evidence than the risk factors mentioned above[56]. Black or Asian race and diabetes mellitus have shown a negative association with the development of AAA[56].

Risk of rupture and indication for intervention

The risk of rupture is associated with the size of the aneurysm. Small aneurysms have a very low risk of rupture, but the larger the aneurysm, the greater is the risk of rupture. When the maximum diameter of the aneurysm exceeds 5.5 cm, the risk of rupture increases markedly[57-59]. Elective surgical repair of non-ruptured AAAs is associated with a mortality of around 1.3–5.8%[60-62]. Given the procedure-related risk of death and the low risk of rupture and death in small aneurysms, it is not beneficial to treat small aneurysms surgically. Two large randomized trials comparing ultrasound surveillance of AAAs measuring 4–5.5 cm

and early surgical repair have been published[62,63]. The studies showed that ultrasonographic surveillance for small abdominal aortic aneurysms is safe, and that surgery does not provide a long-term survival advantage. The results did not support a policy of surgical repair for abdominal aortic aneurysms of 4.0–5.5 cm in diameter. It is generally accepted that elective AAA repair is indicated in patients who are fit for surgery when the maximum diameter of the aneurysm exceeds 5.5 cm. However, it has been observed that women have a higher rupture-related mortality than men[53,64-68], and some authors have advocated a threshold of 5.0 cm for elective repair in women. The procedure-related risk is also higher in women[65,67,69], so patient selection is of importance.

In patients with a ruptured AAA, the mortality rate without surgical intervention is 100%. Thus, rupture is an obvious indication for surgery in patients who are considered to be fit for such a procedure and who have a reasonable chance of surviving both surgical intervention and the perioperative period.

Clinical presentation

Abdominal aortic aneurysms are usually asymptomatic when they have not ruptured, and the sensitivity of abdominal palpation for detection of non-ruptured AAAs is reported to be < 70% or even lower in obese patients[70]. Rupture, on the other hand, is a dramatic event accompanied by massive bleeding, with an overall mortality previously reported to be around 70–80%[71,72]. Many patients who suffer from a ruptured abdominal aortic aneurysm never reach surgery. Ruptured abdominal aortic aneurysms that are not treated with surgical intervention have a mortality of 100% and death normally occurs within hours to days. Occasionally, in contained retroperitoneal ruptures, death might be postponed several weeks.

Sometimes non-ruptured aneurysms can cause symptoms. Abdominal pain and back pain are the most common symptoms. Symptoms from an aneurysm and tenderness on palpation of the aneurysm are considered to

be an indication of a high risk of rupture. Symptomatic aneurysms should therefore be repaired as soon as possible.
The classical clinical picture in patients with ruptured abdominal aortic aneurysms is a triad: abdominal pain, hypotension, and a palpable pulsatile mass in the abdomen. However, many patients with rAAA do not present with the classical triad, and the condition is too often foreseen and the patients misdiagnosed[73-84]. The effect of misdiagnosis on the patient's prognosis is largely unknown.

The mortality in rAAA patients who undergo surgery is only partly explained by intraoperative deaths due to uncontrollable bleeding. Multiple-organ failure, cardiovascular complications, septicaemia, bowel gangrene, and abdominal compartment syndrome are also factors that contribute to in-hospital mortality following rAAA repair.

Imaging

AAAs and rAAA can be identified with different imaging techniques including ultrasound, CT, and MR. Ultrasound is a radiation-free and normally contrast-free method that is suitable for screening and detection of AAAs. A CT scan is often used to more exactly reveal the anatomy of the aneurysm when surgical intervention is considered.

Treatment

Medical treatment

Several drugs have been studied in order to find a medical therapy that can prevent the development and growth of AAAs. So far, no drug has been shown to be beneficial [85,86]. Smoking cessation and adequate treatment of hypertension and other cardiovascular risk factors is offered to patients with small AAAs. The treatment of larger aneurysms is surgical, with two principal surgical techniques available: open repair (OR) and endovascular aortic repair (EVAR).

Surgical treatment

Open repair

OR is a surgical procedure where the abdomen is generally opened in the midline.

The small intestine is held to the right in the abdominal cavity. The retroperitoneum is opened to expose the aneurysm. The aorta is clamped above and below the aneurysm to temporarily inhibit blood flow. The aneurysm sac is opened and a synthetic graft is sutured to the aorta proximally and distal to the aneurysm. The clamps are removed to allow blood flow in the graft. The aneurysm walls are wrapped around the synthetic graft to protect it and prevent infection and formation of aorto-enteric fistulae[87].

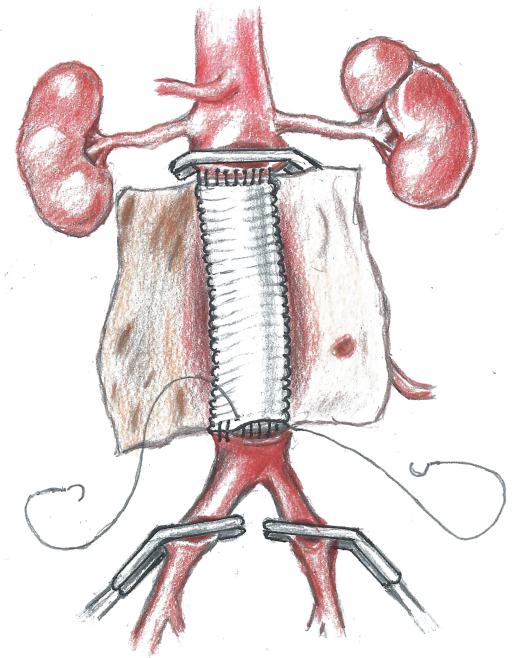

Illustration 1.

The technique used in open repair of an abdominal aortic aneurysm.

EVAR

EVAR is performed percutaneously and can be done under local anaesthesia if necessary. Punctures in the groins give access to the femoral arteries. A covered stent (stent graft) is introduced through the femoral and iliac arteries under radiological guidance. The stent graft is positioned in order to exclude the aneurysm from the circulation. In standard cases with infrarenal aneurysms, the proximal end of the stent graft is positioned just below the renal arteries. The placement of a stent graft requires sealing zones with normal aorta and iliac vessels above and below the aneurysm where the stent graft is anchored.

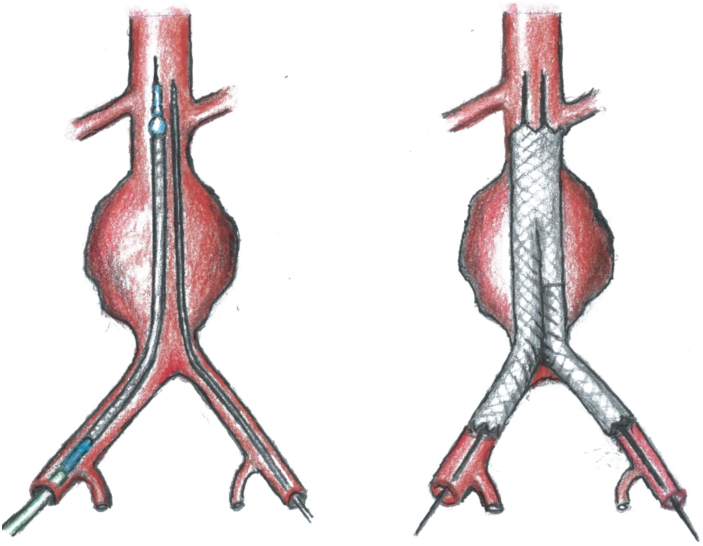

Illustration 2.

Endovascular aortic repair (EVAR). A stent graft is positioned in the abdominal aortic aneurysm under radiological guidance in order to exclude the aneurysm from the circulation.

Outcome of surgical intervention

Elective open repair or EVAR in non-ruptured aneurysms

In large, randomized controlled trials comparing open repair and EVAR (ACE, DREAM, EVAR 1, OVER), short-term mortality has been reported to be 0.6–4.6% in patients treated with open repair and 0.5–1.8% in patients treated with EVAR electively for asymptomatic unruptured aneurysms [88-91]. The results in the studies were similar. There is an initial survival benefit for patients treated with EVAR rather than open repair due to a lower 30-day mortality in EVAR patients. The benefit of using EVAR disappears within a few years. EVAR patients must be monitored with CT or ultrasound for several years or for life, to detect potential endoleaks reperfusing the aneurysm sack—with the risk of late rupture. Re-interventions required for the treatment of endoleaks make the need for reintervention more common in EVAR patients[92,93].

In a 15-year follow-up of the EVAR 1 study, the EVAR group had a higher mortality (with a hazard ratio of 1.25) than the open-repair group beyond 8 years after the procedure, which was mainly attributed to late sac ruptures[94].

The 30-day mortality in patients treated for intact AAAs reported in the Swedish Registry for Vascular Surgery (Swedvasc) in 2016 was 2.4% for patients treated with open repair and 1.7% for patients treated with EVAR[61].

Open repair and EVAR in patients with ruptured abdominal aortic aneurysms

In patients with ruptured abdominal aortic aneurysms (rAAAs), both EVAR and open repair can be performed, depending on the morphology

of the aneurysm and the available expertise. Despite the minimally invasive nature of EVAR and the possibility of avoiding general anaesthesia, randomized controlled trials have failed to demonstrate any significant survival benefit in patients with rAAA who are treated with EVAR rather than open repair. The short-term mortality reported in these randomized trials has been 24–39.1% in the open repair group and 18–36.4% in the EVAR group[95-97].

The 30-day mortality in patients treated for ruptured AAAs reported in the Swedish Registry for Vascular Surgery (Swedvasc) in 2016 was 26% in those treated with open repair and 18% in those treated with EVAR[61].

Mortality in patients undergoing surgical intervention for rAAA is only partly explained by uncontrollable intraoperative bleeding. Cardiopulmonary complications, multiple-organ failure, septicaemia, bowel ischaemia, renal failure, extremity ischaemia, cerebrovascular complications, and abdominal compartment syndrome are also factors that contribute to mortality in patients who have been treated for rAAA.

Abdominal compartment syndrome

The abdomen is a closed cavity. The intra-abdominal pressure (IAP) is approximately the same as atmospheric pressure in young healthy adults in the supine position[98], and 5–7 mmHg in critically ill adults[99]. An increased intra-abdominal pressure above 12 mmHg is called intra-abdominal hypertension (IAH). APP is the abdominal perfusion pressure, which is defined as the mean arterial pressure (MAP) minus the IAP. The standard for the measurement of the IAP is through a catheter in the urinary bladder.

An abdominal compartment syndrome (ACS) arises if the IAH rises to levels at which organ functions are affected. ACS is defined by the World Society of the Abdominal Compartment Syndrome (WSACS) as a sustained IAP of > 20 mmHg (with or without an APP

of < 60 mmHg) that is associated with new organ dysfunction/failure. Intra-abdominal hypertension can affect multiple organ systems, causing an ACS and multiple-organ failure:

The respiratory system

Elevated IAP causes the diaphragm to rise, which leads to a reduced intrathoracic volume. Secondary to this, lung capacity and compliance are reduced. The pulmonary vascular resistance is increased by the elevated intrathoracic pressure, leading to a further reduction in gas exchange. In a porcine model, respiratory dysfunction arose when IAP exceeded 15 mmHg and respiratory failure worsened with increasing IAP[100].

The cardiovascular system

Increasing IAP is accompanied by an increased resistance to blood flow in the vena cava and portal vein, reducing the venous return to the heart. The increased intrathoracic pressure associated with the IAH further reduces venous return in the inferior and superior vena cava. The reduced preload and an increased afterload associated with the IAP reduce the cardiac output[101].

Renal dysfunction

The deterioration in renal function associated with ACS is probably multifactorial, including an impaired renal perfusion associated with a reduced cardiac output and also an increased renal vascular resistance due to compression of the kidneys and renal vein, caused by the IAH[102]. The renin-angiotensin system is activated and contributes to oliguria.

Hepatic dysfunction

Increased IAH reduces the mesenteric and hepatic arterial blood flow and also the portal flow and hepatic microcirculation[102]. In a porcine model

where the IAH was elevated to 15 mmHg for 24 hours, alanine transaminase and alkaline phosphatase levels were elevated and histological examination of the liver showed low-grade necrosis[103]

The gastrointestinal tract

ACS causes decreased mucosal blood flow and intestinal ischaemia, resulting in bacterial translocation.[104]

The central nervous system

The intracranial pressure is increased in patients with ACS. It has been suggested that this may be due to a functional obstruction of the venous outflow from the brain associated with the increased thoracic pressure[105,106].

Abdominal compartment syndrome in patients with rAAA

Incidence and mortality

Given the risk factors for the development of ACS (abdominal surgery, hemoperitoneum, acidosis, polytransfusion, hypothermia, shock or hypotension, coagulopathy, and age[107]), it is not surprising that ACS is common in patients who are treated for rAAA.

ACS has been reported to occur in 6.9–20% of patients treated for rAAA with EVAR and 6.8–34% of patients treated for rAAA with open repair[108-113]. An IAP of > 20 mmHg (with or without a manifest ACS) has been reported to occur in about half of all patients who are treated with open repair for rAAA[114].

The development of ACS is associated with a poor prognosis in patients treated for rAAA. Mayer et al. reported 30% mortality in patients treated with EVAR for rAAA who developed ACS as compared to 8% in

patients who did not develop ACS[110]. In a study by Pecoraro et al., mortality in patients with ACS after open repair for rAAA was 71%, as compared to 23% in those who did not develop ACS[115]. In a population-based Swedish study by Ersryd et al., mortality in patients treated with EVAR or open repair for rAAA was 42.4% in those with ACS and 23.5% in those without ACS[108].

In a study of patients treated for rAAA with either EVAR or open repair, by Sörelius et al., the mortality in patients who needed decompression for ACS was 62%, as compared to 29% in patients who did not develop ACS[116].

ACS occurs more seldom in patients who are treated for intact AAAs (iAAAs): in 0.4–0.5% of patients treated with EVAR and in 0.9–1.6% of patients treated with open repair[108,116]. When ACS occurs after surgical intervention for iAAA, the mortality has been reported to be as high as 11.5% (as compared to 1.8% in those who did not develop ACS[108]).

Treatment

Several medical and non-invasive treatments have been proposed for the treatment of ACS, including sedation/analgesia, neuromuscular blockade, nasogastric/colonic decompression, promotility agents, and avoidance of positive cumulative fluid balance. However, decompressive laparotomy should be performed in cases of overt ACS according to current guidelines[107].

The potential benefit of avoiding the possibility of development of ACS by leaving the abdomen open with a vacuum-assisted wound closure system and delayed closure has not been studied thoroughly.

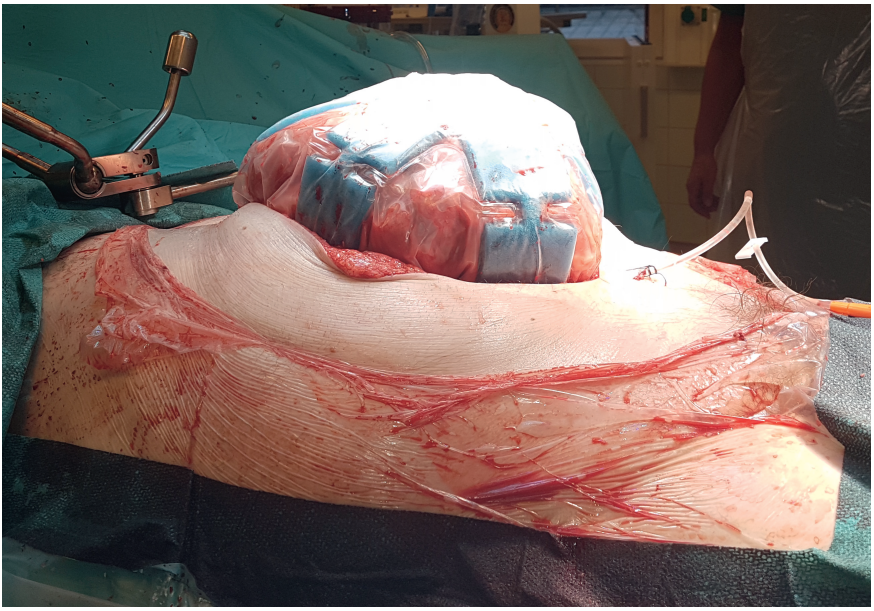

Illustration of massive swelling of the abdominal viscera in a patient treated with open repair for a ruptured abdominal aortic aneurysm. The abdomen was left open with a vacuum-assisted closure dressing to avoid development of an abdominal compartment syndrome.

Screening

AAAs are generally asymptomatic before rupture. Elective repair of intact AAAs is associated with a relatively low mortality (the contemporary 30-day mortality after elective surgical intervention is approximately 2.0% in Sweden)[61] while rupture is associated with a total mortality reported to be 68-85%[71,72,117]. Thus, it is beneficial to detect aneurysms before rupture. AAAs can easily be detected with ultrasonography. These considerations would suggest that AAA is a disease suitable for screening. In fact, AAA fulfils all the classic criteria for screening proposed by Wilson and Jungner[118].

Accordingly, screening for AAA has been studied thoroughly. Four randomized controlled studies of population screening for rAAA were

performed in the 1990s: the Chichester trial in the UK[119], the Viborg trial in Denmark[120], the Multicentre Aneurysm Screening Study (MASS) in the UK[121], and the Western Australia trial[122]. Early results showed a reduction in aneurysm-related mortality of approximately 40% in men who were invited to screening. Long-term results are now available for all four studies, and a meta-analysis by Takagi et al. of the late results of all trials was recently published[123]. It shows that inviting men for AAA screening reduces AAA-related deaths (OR 0.66, 95% CI 0.47–0.93; p = 0.02), with a greater effect on men who attend the program (OR 0.40, 95% CI 0.31–0.51; p < 0.00001. It was also found that screening reduced all-cause mortality in invited men (HR 0.98, 95% CI 0.96–0.99; p = 0.003).

The evidence base for population-based screening of AAA in elderly men is solid, and population screening of 65-year-old men has been started in Sweden and now has nationwide coverage. The outcome of the Swedish screening program has been reported by Wanhainen et al[30]. The prevalence of AAA was found to be 1.5% and the number needed to be screened to prevent one premature death from AAA was 667. It was predicted that the screening programme prevents 90 premature deaths from AAA annually in Sweden.

The results of surgical intervention in patients with screening-detected aneurysms (compared to the previous standard vascular surgery patient with an AAA that was not detected by screening) have not been studied thoroughly.

AAA screening in women

Only one of the randomized studies [119] included women. Given the low prevalence of AAA and the low incidence of rupture in women, it was concluded that screening of women would be unlikely to affect the outcome of the disease significantly. In a Swedish screening study investigating the prevalence of AAA in 70-year-old women, the prevalence was found to be 0.5%[37]. A strong correlation was seen

between smoking and AAA. In women who had never smoked, the prevalence of AAA was as low as 0.03%. It was concluded that screening of non-smoking women would be futile, ruling out population-based screening in women. There is no current evidence to support population-based screening of women for AAA.

AIMS

Overall aim

To investigate possible ways to reduce mortality from ruptured abdominal aortic aneurysms.

Specific aims

- To compare the postoperative outcome in patients treated for abdominal aortic aneurysms that were detected by screening with that in patients treated for aneurysms that were not detected by screening, in a population-based setting (Study 1).
- To investigate the frequency of misdiagnosis of ruptured abdominal aortic aneurysms in the emergency department and how misdiagnosis affects the prognosis in terms of mortality and complications (Studies 2 and 4).
- To investigate whether it is beneficial to treat patients operated with open repair for a ruptured abdominal aortic aneurysm with a primary open abdomen and delayed closure in order to avoid the possibility of development of an abdominal compartment syndrome, and the increased mortality and rate of complications associated with this condition (Study 3).

Patients and methods

Table 1. Overview of study design, number of participants, data sources, comparison, and outcome

	Design	n	Source	Comparison	Outcome
Study 1	Prospective cohort study	700	Swedvasc	Detected by screening vs. not detected by screening	Mortality and complications after surgical intervention
Study 2	Retrospective cohort study	261	Swedvasc and medical records	Misdiagnosed vs. correctly diagnosed	Mortality and complications after surgical intervention
Study 3	Retrospective cohort study	227	Swedvasc and medical records	Primary open abdomen treatment vs. primary abdominal closure	Mortality and complications after surgical intervention
Study 4	Retrospective cohort study	455	Swedvasc, Swedish Cause of Death Registry, medical	Misdiagnosed vs. correctly diagnosed	Mortality

Sources of data

Swedvasc

All the studies in this thesis used data extracted from Swedvasc. In study 1, Swedvasc data alone were used, and in Studies 2–4, Swedvasc data were combined with other sources of data.

Swedvasc is the Swedish National Registry for Vascular Surgery. The registry was started and is still maintained by the vascular surgery profession in Sweden. The registry achieved nationwide coverage in 1994, including all vascular surgery centres in Sweden. Data are registered prospectively, usually by the vascular surgeon performing the procedure, but some hospitals have appointed staff to perform registrations. Swedvasc has data on vascular procedures including individual patient data (age, sex, comorbidities, whether an aneurysm was detected by screening) and also procedural, follow-up, and mortality data. The registry does not contain any information on patients with vascular diseases who have not undergone a vascular procedure. Swedvasc is cross-linked to the Swedish Population Registry, making mortality data in the registry highly accurate.

An international validation of data registered in Swedvasc was performed by two independent validators, M. Venermo (Finland) and T. Lees (UK) in 2014. Local hospital records for 2012 from five vascular centres in Sweden were crosschecked with data registered in Swedvasc. It was checked whether all the procedures performed at the centres were registered in Swedvasc (external validity) and whether the data recorded in Swedvasc were accurate (internal validity). Regarding AAA procedures, the external validity was found to be 98.8% (95% CI 96.9–99.5) and the internal validity was 96.2% (95% CI 94.9–97.2). Four of 393 AAA procedures registered in the hospital records were not registered in Swedvasc. Mortality in these patients was checked, to rule out the possibility that the reason they were not registered was a bad

outcome. The four patients were all found to be alive in 2014. It was concluded that Swedvasc is a highly accurate system of data collection for Swedish vascular surgery[124]. In an earlier (2008) validation study of Swedvasc by Troëng et al., the external validity for abdominal aortic aneurysm repairs was found to be 93.2%. The study showed no significant difference in mortality between registered patients and the whole cohort in elective cases. A higher mortality was observed in unregistered patients treated with emergency (unplanned) open repair than in patients registered in Swedvasc. However, when the unregistered cases were added to the registered cases, no significant increase in mortality in the whole cohort was observed. It was concluded that the external and internal validity of the Swedvasc registry allows confident assessment of volumes of—and mortality after—vascular surgery in Sweden[125].

In conclusion, Swedvasc is a registry that is considered to have a high validity, which has been confirmed by external analysis. The Swedish Association of Local Authorities and Regions has a grading of the Swedish quality registries, giving the registries a certification level. The certification level is a rating given to each registry and represents the level of development that the registry has reached in terms of analyses, inclusion of relevant indicators, coordination with health services, use in research, data quality and reporting, coverage rate, technical solutions/tools, and so on. There are four certification levels, with 1 being the highest. Swedvasc has certification level 1.

Several scientific reports using Swedvasc data have been published, and 15 PhD theses have used Swedvasc data.

The Swedish Cause of Death Registry

Data from the Swedish Cause of Death Registry were used in Study 4. The Cause of Death Registry includes all those who died during one calendar year and were registered in Sweden at the time of death. The cause of death and disease(s) contributing to the cause of death are registered according to the international version of the disease classification ICD-10. The Swedish personal identification number of deceased persons is included in the registry, allowing cross matching with other registries.

Medical charts

Data extracted through review of medical charts were used in Studies 2–4. All medical charts in Västra Götaland Region during the time period of the studies in this thesis were electronic, including notes, laboratory data, and radiological examinations. Pre-hospital data on patients transported with emergency services were also available in the individual patient's charts. In Study 3, medical charts were retrieved from other vascular centres by post, for the propensity score-matched control group.

Study design, subjects, and endpoints

Study 1

This was a prospective cohort study using prospectively collected data in Swedvasc. Men with AAAs detected through population-based screening were compared to an age-matched control group consisting of men with AAAs that were not detected by screening, for the period May 2010 to January 2013. The hypothesis was that men with screening-detected aneurysms would have a better outcome after surgical intervention than men with aneurysms that were not detected by screening, due to there being less comorbidity. The main aim was to compare the postoperative outcome after elective surgical intervention in terms of mortality and the frequency of complications at 30 days in men with screening-detected AAAs and in men with AAAs that were not detected by screening. Secondary aims were to compare 90-day and 1-year mortality, preoperative comorbidity, and choice of surgical method between the groups. The primary endpoint was a combined endpoint consisting of mortality, myocardial infarction, stroke, major amputation, bowel ischaemia, and renal failure within 30 days after the surgical intervention.

Study 2

This study was a retrospective cohort study comparing the outcome in patients with rAAA who were misdiagnosed at the first assessment in the emergency department with patients who were correctly diagnosed. Patients treated with surgical intervention for rAAA in Västra Götaland Region in the period 2008–2014 were identified in Swedvasc. Only patients who were correctly diagnosed some time in the chain of care and then underwent surgical or endovascular treatment for rAAA were included. Prospectively registered baseline data regarding age, sex, comorbidities, and type of surgical intervention (open repair or EVAR)

were extracted from Swedvasc. The data extracted from Swedvasc were combined with data extracted from medical charts, including data regarding assessment in the emergency department. Pre-hospital data and time parameters were also extracted from the medical charts.

We hypothesized that initially misdiagnosed patients have a higher mortality and a higher frequency of complications than patients who are correctly diagnosed initially. The aim of the study was to investigate how common it is that patients with rAAA are misdiagnosed and how misdiagnosis affects the outcome in rAAA patients. The primary endpoint was 30-day mortality. Secondary endpoints were 90-day mortality, need for ventilator support, need for postoperative haemodialysis, days in the intensive care unit (ICU), and length of hospital stay. In addition, delay caused by misdiagnosis was recorded.

Study 3

This was a retrospective cohort study comparing mortality and postoperative complications in patients treated initially with an open abdomen and delayed closure after open repair for rAAA with those in a propensity score-matched control group where the abdomen was closed at the end of the procedure in a majority of the cases. The reason for leaving the abdomen open would be to avoid the risk of development of an abdominal compartment syndrome (ACS) and the increased mortality and morbidity associated with this (as described in the Introduction section). For several years, it has been a clinical routine at Sahlgrenska University Hospital to leave the abdomen open at the end of open repairs for rAAA, except in selected cases with stable patients and limited haematomas. This has led to an accumulated list of cases with open abdomen treatment, allowing comparison with controls. Propensity score matching was used to create a control group from other vascular centres in Sweden, using patients registered in Swedvasc. Baseline data including age, sex, aneurysm diameter, perioperative bleeding, and

comorbidities, and also mortality data, were extracted from Swedvasc. Medical records were retrieved and data regarding clamp position (suprarenal or infrarenal) and complications were extracted from the medical charts.

We hypothesized that open abdomen treatment and delayed closure would be associated with a lower mortality and less complications than primary closure of the abdomen in patients who undergo open repair for rAAA. The aim of the study was to investigate whether leaving the abdomen open, with delayed closure, would improve outcome in terms of mortality and complications in patients treated for rAAA with open repair. The primary endpoint was 30-day mortality. Secondary endpoints were 90-day mortality, bowel ischaemia, need for postoperative renal replacement therapy, and postoperative bleeding requiring surgery.

Study 4

This was a retrospective cohort study comparing mortality in rAAA patients who were misdiagnosed in the emergency department with patients who were correctly diagnosed. In contrast to Study 2, all patients with rAAA seeking treatment in an emergency department in Västra Götaland Region were eligible for inclusion, not only patients who reached surgical intervention. Data on patients treated surgically for rAAA in Västra Götaland Region in the period 2010–2015 were extracted from Swedvasc and data on patients registered in the Swedish Cause of Death Registry with rAAA as the cause of death were also extracted. All deaths recorded in the Swedish Cause of Death Registry were confirmed by review of the medical records and/or autopsy reports. Data regarding the assessment in the emergency department and clinical parameters were extracted from the medical records.

We hypothesized that misdiagnosis in the emergency department in patients with rAAA would be associated with a higher mortality than in

patients who are correctly diagnosed. The aim of the study was to test this hypothesis. The endpoint was rAAA-related mortality.

Statistics

All statistical analysis in this thesis was performed using the Statistical Package for the Social Sciences (SPSS; IBM Corp. Armonk, NY, USA). SPSS 22.0 was used in study 1 and SPSS 23.0 was used in Studies 2–4. Descriptive statistics for baseline data are presented as mean ± standard deviation (SD) or as median and inter-quartile range (IQR). Fisher's exact test was used for inter-group comparisons of dichotomous variables. Student´s t-test was used for two-group comparison of means. Mann-Whitney U-test was used when assumptions of normality were violated. Univariate binary logistic regression analysis and multivariable binary logistic regression analysis were used in all studies in order to adjust for confounders that could possibly influence the outcome. Propensity score matching was used in Study 3. The propensity score was based on nearest-neighbour analysis with two controls for each patient. The controls were matched with respect to age, gender, perioperative blood loss, preoperative unconsciousness, serum creatinine level, and the preoperative comorbidities cardiac disease, hypertension, diabetes, respiratory disease, and history of a cerebrovascular event.

Ethical considerations

The four studies in this thesis all investigated outcomes after different actions and procedures already performed by the healthcare system in Sweden. Thus, the studies did not put any patients at risk of physical

harm. Review of medical records violates the integrity of individuals to some extent. This potential psychological harm was considered to be outweighed by the advantage of gaining important knowledge about the treatment of abdominal aortic aneurysms. One could argue that it would have been unethical to refrain from evaluating the results of a screening programme implemented in a particular country (which was done in Study 1). It could also be considered unethical not to investigate the results of open abdomen treatment after open repair for rAAA (which was done in Study 3), given the very limited knowledge and evidence that exists on the topic, and the fact that open abdomen treatment has been a clinical routine at Sahlgrenska University Hospital for several years. The studies in this thesis were considered to be ethically sound. Ethical permission for Study 1 was obtained from the regional ethics committee in Uppsala (entry no. 2012/282) and ethical permission for Studies 2–4 was obtained from the Regional Ethical Review Board in Gothenburg (entry no. 553-14).

Results

Study 1

Three hundred and fifty operated men with screening-detected AAAs were compared to 350 operated controls with AAAs that were not detected by screening. There were no significant differences in baseline data except that the median age was 2 years older in patients whose AAAs were not detected by screening. The rate of postoperative complications was low in both patients with screening-detected AAAs and patients with AAAs not detected by screening. No significant difference in the rate of complications, in mortality at 30 days, and in the combined primary endpoint (mortality and major complications at 30 days) was observed between the two groups when stratified into open repair and EVAR (Table 2). Multivariable logistic regression analysis adjusted for age and method of intervention showed no increased risk of death or major complications in patients with non screening-detected aneurysms (OR 1.64, 95% CI 0.82–3.25).

There was no difference in 30-day or 1-year mortality between patients with screening-detected aneurysms and the age-matched controls with aneurysms that were not detected by screening. Mortality at 90 days in patients treated with EVAR was higher in control patients than in patients whose aneurysms were detected by screening (3.1% vs. 0%; $p = 0.04$), but there was no significant difference between the groups in patients treated with open repair. When we included both patients treated with open repair and patients treated with EVAR, the 90-day mortality was lower in patients with screening-detected aneurysms than in control patients (1.1% vs. 3.7%; $p = 0.046$).

Mortality data are presented in Table 3.

In multivariable logistic regression analysis adjusted for age and method of intervention (EVAR or open repair), there was an increased risk of death at or before 90 days for patients with aneurysms that were not detected by screening (OR 3.31, 95% CI: 1.05–10.46).

Open repair was used more frequently in screening-detected patients (56%) than in patients whose aneurysms were not detected by screening (45%) ($p < 0.01$)

Table 2. Comparison of complications 30 days after surgery in screening-detected AAA patients and in age-matched controls with non screening-detected AAAs n = 663-700 (varies with outcome due to missing data) excluded due to missing data)

Complications 30 days after surgery	Open repair			EVAR		
	Screening-detected n (%)	Non-screening-detected age-matched controls n (%)	p	Screening-detected n (%)	Non-screening-detected age-matched controls n (%)	p
	186	147		147	183	
Death	2 (1.0)	5 (3.2)	0.25	0 (0)	0 (0)	1.00
AMI	4 (2.2)	2 (1.4)	0.70	0 (0)	2 (1.1)	0.50
Stroke	2 (1.1)	3 (2.0)	0.66	1 (0.7)	1 (0.5)	1.00
Amputation	0 (0)	1 (0.7)	0.44	0 (0)	0 (0)	1.00
Bowel ischaemia	1 (0.5)	1 (0.7)	1.00	0 (0)	0 (0)	1.00
Renal failure	7 (3.7)	8 (5.4)	0.60	2 (1.4)	5 (2.7)	0.47
Combined endpoint*	*12 (6.4)*	*16 (10.6)*	*0.17*	*3 (2.0)*	*7 (3.8)*	*0.52*
Abd compartment	6 (3.2)	6 (4.1)	0.77	2 (1.4)	0 (0)	0.20
Distal embolization	5 (2.7)	5 (3.4)	0.75	2 (1.4)	2 (1.1)	1.00
Reop. bleeding	2 (1.1)	4 (2.7)	0.41	1 (0.7)	5 (2.7)	0.23

AMI, acute myocardial infarction.

*Combined endpoint—any of the following: death, AMI, stroke, major amputation, bowel ischaemia, renal failure.

Table 3. Mortality after open repair and endovascular aortic repair (EVAR) in screening-detected AAA patients and in age-matched control patients in whom aneurysms were not detected by screening

Mortality	Open repair (n = 352)			EVAR (n = 348)			All (n = 700)		
	Screening-detected n (%)	Non-screening-detected n (%)	p	Screening-detected n (%)	Non-screening-detected n (%)	p	Screening-detected n (%)	Non-screening-detected n (%)	p
n	195	157		155	193		350	350	
30-day	2/195 (1.0)	5/157 (3.2)	0.25	0/155 (0)	0/193 (0)		2/350 (0.6)	5/350 (1.4)	0.45
90-day	4/195 (2.1)	7/157 (4.5)	0.23	0/155 (0)	6/193 (3.1)	0.04	4/350 (1.1)	13/350 (3.7)	0.046
1-year	7/173 (4.0)	9/155 (5.8)	0.61	2/140 (1.4)	9/191 (4.7)	0.13	9/313 (2.9)	18/346 (5.2)	0.17

AAA, abdominal aortic aneurysm.

Study 2

Two hundred and sixty-one patients with rAAA were included in the study. Eighty-six (33%) were initially misdiagnosed. Baseline data showed no significant differences between the groups apart from a higher proportion of patients with a first systolic pressure < 90 mmHg in the correctly diagnosed group than in the misdiagnosed group (37.0 vs. 12.8%; $p < 0.001$). Misdiagnosis caused a median delay until surgical treatment of 4.8 hours. There was no significant difference in 30- or 90-day mortality, rate of complications, length of intensive care, or length of hospital stay between misdiagnosed and correctly diagnosed patients (Table 4).

Multivariable logistic regression analysis was performed, with adjustment for the potential confounders age, sex, open repair/EVAR, primary assessment by internist/surgeon, respiratory disease, and transportation to secondary hospital. In this analysis, the OR for mortality at 30 days was 0.78 (95% CI 0.38–1.60) in misdiagnosed patients compared to correctly diagnosed patients. The adjusted OR for death at 30 days in women was 2.32 (95% CI: 1.15–4.67). The multivariable logistic regression analysis is shown in Table 5

Table 4. Mortality, need for postoperative dialysis, days in ventilator, days in ICU, length of hospital stay, and proportion of patients who were able to return to their own home at discharge

	Correct diagnosis, n (%)	**Misdiagnosis, n (%)**	**p**
30-day mortality	49(28.0)	24(27.9)	1.00
90-day mortality	57(32.6)	32(37.2)	0.49
Need for postoperative haemodialysis	35(22.0)	16(20.5)	0.87
Days in ventilator*	1(1-5)	1.5(0-6)	0.90
Days in ICU*	4(2-11)	3.5(2-9)	0.73
Length of hospital stay, days*	14(6-32)	14(8-23.5)	0.77
Discharged to own home	99(56.6)	48(55.8)	1.0

*Median (IQR).
ICU, intensive care unit.

Table 5. Mortality at 30 days in patients with a ruptured abdominal aortic aneurysm

	OR, crude mortality at 30 days	95% CI	p[a]	OR, adjusted mortality at 30 days[b]	95% CI
Misdiagnosis	1.0	0.56–1.77	0.99	***0.78***	***0.38–1.60***
Age (per year) (missing = 0)	1.05	1.01–1.09	0.02	1.05	1.00–1.10
Females (missing = 0)	2.07	1.13–3.80	0.02	2.32	1.15–4.67
OSR (compared with EVAR) (missing = 0)	1.99	0.97–4.08	0.06	1.76	0.75–4.15
Transportation to secondary hospital (missing = 0)	0.63	0.36–1.12	0.11	0.59	0.30–1.18
Respiratory disease (missing = 28)	2.11	1.10–4.04	0.02	1.95	0.95–4.02
First assessment by internist (compared with surgeon) (missing = 21)	2.11	1.12–4.00	0.02	2.01	0.94–4.28
Previous heart condition (missing = 24)	1.61	0.90–2.90	0.11		
Previous TIA/stroke (missing = 28)	0.88	0.36–2.19	0.79		
Creatinine > 150 µmol/L (missing = 8)	1.44	0.73–2.84	0.29		
Hypertension (missing = 51)	1.95	0.91–4.20	0.09		
First-recorded BP ≤ 90 mmHg (compared with > 90 mmHg) (missing = 2)	1.08	0.60–1.96	0.79		
Reported syncope (missing = 0)	0.91	0.53–1.58	0.75		

OR, odds ratio; CI, confidence interval; OSR, open surgical repair; EVAR, endovascular aortic repair; TIA, transient ischaemic attack; BP, blood pressure.
[a]p-values for the univariate analysis.
[b]Multivariate logistic regression analysis adjusted for misdiagnosis/correct diagnosis, age, sex, open repair/EVAR, primary assessment by internist/surgeon, respiratory disease, and transportation to secondary hospital.

Study 3

Altogether, 227 patients treated with open repair for rAAA were included in the study. Seventy-nine patients treated with primarily open abdomen after open repair at Sahlgrenska University hospital were compared to 148 propensity score-matched controls treated at other vascular centres in Sweden. Medical records for control patients were retrieved after the propensity score matching. After review of these medical records, it was found that 40 (27%) of the patients in the control group were treated with open abdomen initiated at the primary operation. Thus, in the analysis, a cohort of patients who were all treated with a primary open abdomen was compared to a group where a clear majority (n = 108, 73%) were treated with a primary closed abdomen. There were no other differences in baseline data between the groups.

There was no significant difference in mortality at 30 or 90 days, in need for renal replacement therapy, in frequency of bowel ischaemia, or in need for reoperation due to bleeding between the groups (Table 6).

The adjusted odds ratio for mortality at 30 days was 0.66 (95% CI: 0.35–1.25) in patients treated with a primary open abdomen after open repair for rAAA at Sahlgrenska University Hospital (compared to the controls). Potential confounders that were adjusted for in the analysis were age, sex, perioperative bleeding > 5,000 ml, and creatinine > 150 mmol/l.

Early graft infection occurred in 5.1% of the patients who were treated with open abdomen at Sahlgrenska University Hospital, as compared to 2% in the control group (p = 0.24).

Table 6. Thirty-day mortality, need for postoperative haemodialysis, and intestinal ischaemia requiring bowel resection in patients treated with primary open abdomen at Sahlgrenska University Hospital, compared to propensity score-matched controls from other vascular centres in Sweden where open abdomen treatment was not a clinical routine (the abdomen was closed in 73% at the end of the primary procedure and left open in 27% of the control patients)

	Patients treated for rAAA with a primary open abdomen at Sahlgrenska University Hospital n = 79	**Controls n = 148**	**p**
Thirty-day mortality	21 (26.6%)	49 (33.1%)	0.37
Ninety-day mortality	27 (34.2%)	54 (36.7%)	0.77
Postoperative renal failure with need for renal replacement therapy	25 (31.6%)	39 (26.4%)	0.44
Postoperative intestinal ischaemia requiring bowel resection	7 (8.9%)	21 (14.2%)	0.29
Reoperation due to bleeding	5 (6.3%)	22 (14.9%)	0.08

rAAA, ruptured abdominal aortic aneurysm.

Study 4

Altogether, 455 patients seeking care in an emergency department for a confirmed rAAA were included in the study. Two hundred and forty-eight patients underwent surgical intervention and 207 did not. At baseline, a systolic blood pressure of < 90 mmHg was more frequent in the correctly diagnosed group and the mean S-creatinine level was higher in the correctly diagnosed group. There were no significant differences between misdiagnosed patients and correctly diagnosed patients regarding mean age or the proportion of women.

One hundred and seventy-seven (38.9%, 95% CI 34.4–43.4%) were initially misdiagnosed. An equal rate of misdiagnosis occurred in women and men. Misdiagnosis was more frequent in patients with a first-recorded systolic blood pressure of > 90mmHg than in patients with a first-recorded systolic blood pressure of < 90mmHg (44.1% vs. 27.9%; p=001).

Abdominal pain, back pain, and syncope were more frequently reported by patients who were correctly diagnosed. Vomiting and dyspnoea were more common symptoms in the misdiagnosed group.

A higher mortality was found in patients who were initially misdiagnosed than in correctly diagnosed patients. When patients who were not offered surgical intervention after detection of a rAAA (palliative patients) were excluded, mortality remained significantly higher in misdiagnosed patients (Table 7).
In multivariable logistic regression analysis adjusted for the potential confounders age, sex, first blood pressure < 90 mmHg, and the level of S-creatinine, the risk of dying from rAAA was higher in misdiagnosed patients than in correctly diagnosed patients (OR 1.83, 95% CI: 1.13–2.96; p = 0.013) (Table 8).

Table 7. Mortality in patients who sought care for a ruptured abdominal aortic aneurysm, according to whether or not they were correctly diagnosed

	Misdiagnosed group	Correctly diagnosed group	p
Mortality in patients who sought care for rAAA (n = 455)	132/177 (74.6%)	175/278 (62.9%)	0.01
Mortality in rAAA patients, palliative patients excluded (n = 321)	84/129 (65.1%)	89/192 (46.4%)	0.001

rAAA, ruptured abdominal aortic aneurysm.

Table 8. Mortality in patients who sought care for a ruptured abdominal aortic aneurysm (n = 455)

	Odds ratio for crude rAAA mortality	95% CI	p-value	Odds ratio for adjusted rAAA mortality*	95% CI	p-value
Misdiagnosis	1.73	1.14–2.62	0.013	1.83	1.13–2.96	0.013
Age (per year)	1.09	1.06–1.12	< 0.0001	1.09	1.06–1.12	< 0.0001
Females	1.99	1.25–3.16	0.004	1.79	1.07–3.00	0.03
First-registered SBP ≤ 90 mmHg	1.13	0.74–1.74	0.58	1.21	0.74–1.99	0.45
Creatinine (per mmol)	1.00	1.00–1.01	0.034	1.00	1.00–1.01	0.03

SBP, systolic blood pressure; CI, confidence interval.
*Multivariable logistic regression analysis adjusted for misdiagnosis/correct diagnosis, age, sex, first-recorded blood pressure, and creatinine level.

Methodological considerations – limitations

Selection bias

In **Study 1,** all patients with screening-detected aneurysms registered in Swedvasc were compared to a matched control group. The risk of any selection bias in **Study 1** was considered to be limited.

In **Study 3,** the patients treated with a primary open abdomen at Sahlgrenska University Hospital were a selection of rAAA patients who were generally unsuitable for EVAR. Furthermore, stable patients with contained haematomas had the abdomen closed at the end of the primary procedure in the study period. Thus, the patients treated with open repair at Sahlgrenska University Hospital in **Study 3** were a selection of patients with unfavourable aneurysm anatomy, a large amount of blood loss, and pronounced circulatory instability. Propensity score matching was used to create a control group resembling this selection as much as possible. However, it cannot be ruled out that there might be a remaining selection unaccounted for in the analysis.

In **Studies 2 and 4**, there was a lower proportion of patients with a first-recorded systolic blood pressure of < 90 mmHg in the misdiagnosis group than in the correct diagnosis group. This indicates that the misdiagnosis group was a selection of more haemodynamically stable patients. Such a selection would have the potential to dilute the result in these two studies, since it is likely that hypotension is associated with worse outcome.

During **Study 4**, we identified patients who had undergone attempts at surgical intervention that were not registered in Swedvasc. This would introduce the possibility of selection bias in **Study 2** (where all the

patients were identified in Swedvasc). It appears unlikely that such selection would be asymmetrically allocated to the misdiagnosis or correct diagnosis groups, so this probably did not contribute to selection bias.

The autopsy rate was 11% in Sweden in 2016, according to the Swedish Cause of Death Registry. This number includes both clinical and forensic autopsies. The low frequency of autopsies might possibly have introduced bias in **Study 4.** There may have been patients who were misdiagnosed and sent home from the ED, and then died from rAAA. If no autopsy was performed in such cases, there would be a risk that the death would be classified as not being aneurysm-related in the Swedish Cause of Death Registry. Such patients would not have been identified and included in **Study 4**, despite seeking care in an ED for rAAA, since those who died from rAAA were identified in **Study 4** by being coded as aortic aneurysm-related deaths in the Swedish Cause of Death Registry. It seems unlikely that this potential bias would be of such a magnitude that it would influence the result, but if this was the case, additional deaths would be added to the misdiagnosis group (but not to the correct diagnosis group). This would strengthen the result in **Study 4** further.

Information bias

Registry studies always have a certain risk of bias due to erroneous registrations in the registry leading to misclassification. Mortality data are considered to be highly accurate, given the interconnection between Swedvasc and the Swedish population registry. Data regarding the type of procedure performed are unlikely to be erroneous. Registration of comorbidity and preoperative parameters in Swedvasc may be erroneous to a certain degree, given the acute character of the disease and the sometimes limited possibility of collecting these data. Swedvasc data regarding comorbidities and preoperative data were used in **Studies 1, 2,**

and 3. Thus, there might be misclassification of confounders to some extent in these studies, but if present, misclassification is believed to be non-differential. The risk of misclassification of treatment or outcome is probably limited.

Review of medical records has an inherent risk of misclassification. Most of the data collected by means of review of medical charts were checked by at least two independent observers in order to minimize this bias, and if present, it is believed to be limited and non-differential.

Confounding

Non-randomized observational studies always have a risk of confounding. In order to minimize this bias, multivariable logistic regression analysis was used in all studies in order to account for known confounders. In **Study 3**, propensity score matching was also used to minimize confounding. Still, there may have been unknown confounders and residual confounding that were unaccounted for in the analysis.

Power

It cannot be ruled out that parts of the results in **Study 1** were the result of type-2 error due to lack of power. This bias was probably not present in **Studies 2–4**.

Discussion

General discussion

The principal aim of research regarding abdominal aortic aneurysms is to investigate possible ways of reducing mortality caused by rupture of the aneurysm. Ideally, some way of preventing the very emergence of an aneurysm—or at least growth of an existing aneurysm—would be the best approach to achieve this goal. Apart from risk factor modification such as reduction of smoking in the community, no efficient way to prevent aneurysm formation or growth is known. The aetiology of the disease is still too poorly understood to allow treatment or actions that would efficiently prevent aneurysm formation or growth in certain individuals. In the work that contributed to this thesis, we studied possible ways of reducing aneurysm-related mortality once an aneurysm has developed. The disease and the treatment of the disease were studied from three different angles representing three different parts of the course of the disease: surgical treatment before rupture, the assessment of patients suffering from a ruptured abdominal aortic aneurysm in the emergency department, and whether it would be possible to reduce the perioperative mortality in rAAA patients by leaving the abdomen open, with delayed closure, in those treated with open repair.

Before rupture

Since rupture of an abdominal aortic aneurysm carries a high mortality no matter what actions are taken by medical staff, it is obvious that it would be beneficial to find aneurysms before rupture, given the possibility of safe surgical treatment of large aneurysms in an elective setting. There is solid evidence from randomized controlled trials (RCTs) that screening for AAA reduces both AAA-related and all-cause mortality in elderly men[119-123]. However, at the time of **Study 1,** there were few published results on outcome after surgery on screening-detected aneurysms under normal clinical circumstances (outside

randomized clinical trials). Prior to screening, most AAAs were detected coincidentally when imaging was performed in patients seeking care for a symptom. A patient cohort seeking care for a symptom could possibly be different from screened patients, since the very fact that they sought medical advice could indicate that they suffered from comorbidities to a greater degree.

Screening was started locally in Sweden in 2006, and reached nationwide coverage in 2015[30]. In 2010–2013, the time period of **Study 1**, vascular surgeons were encountered by an increasing proportion of patients with AAAs detected by screening as compared to the previous standard patient with a coincidentally detected AAA. The contemporary results of surgical intervention for screening-detected aneurysms (compared to aneurysms that were not detected by screening) were not studied. Theoretically, AAA patients detected by screening could have less comorbidities and thus a better prognosis than AAA patients who are not detected by screening. It was also being debated which method of surgical intervention (open repair or EVAR) should be used in the relatively young AAA patients who are detected by screening. When considering surgical intervention, both the surgeon and the patient require better knowledge about the mortality and frequency of complications associated with the surgical intervention.

In **Study 1**, population-based contemporary results of AAA surgery in Sweden were compared between screening-detected patients and age-matched controls whose AAA was not detected by screening. It was found that mortality and the frequency of complications were low in both patient groups. No significant differences in mortality at 30 days or in the rate of complications were found between the groups. The 90-day mortality was higher in non screening-detected patients, and also with adjusted analysis. However, the mean age was 2 years older in the control group, which requires caution when interpreting the results. This difference had to be accepted in the matching procedure in order for us to have a sufficient number of control patients. Not allowing this range in age would have reduced the size of the cohorts and the power.

We hypothesized in **Study 1** that screening-detected patients would have less comorbidity than patients with non screening-detected aneurysms. This could not be verified in the study, as the comorbidity profile was similar in the two groups. Despite this, open repair was used more frequently in screening-detected AAA patients (56%) than in those who were not detected by screening (45%) ($p < 0.01$). This might reflect a preconceived idea among surgeons that screening-detected patients have less comorbidity and are better fit for open surgery than patients who are not detected by screening, and that open surgery might be a better option, as lifelong surveillance after an EVAR is avoided.

When **Study 1** was carried out, all the data available on patients treated for screening-detected AAAs was used, but given the low mortality and the low rate of complications, the numbers of patients who died or suffered from severe complications were low in both groups. This is encouraging, but the low number of events limited the possibility of analysing potential differences between the groups and adjusting for confounders. It cannot be ruled out that the absence of differences between the groups (apart from 90-day mortality) can be explained by type-2 error due to lack of power. However, despite this, the data are important since the nationwide screening will probably make further comparisons between screening-detected and non-screening-detected patients impossible due to the lack of age-matched controls with aneurysms that are not detected by screening. The gradual implementation of the screening programme, which covered the years of Study 1, was a unique opportunity to compare screened and non-screened patients.

To detect a significant difference of 0.8% (the difference in 30-day mortality between the groups), the study would have required a sample size of approximately 2,400 patients in each group. This number of age-matched patients is not available.

An important finding in this contemporary study was the low mortality in patients with screening-detected (0.6%) and non-screening-detected AAAs (1.4%). Subsequent studies of the nationwide results of AAA

screening in England and Sweden have also shown very low perioperative mortality rates (0.8–0.9%)[30,126], results that lend further support to AAA screening in elderly men.

The declining prevalence of AAA and the reduced benefit associated with a lower prevalence—as well as the risk of overdiagnosis and potential psychological harm caused by screening—have been under debate in recent years[127-129]. The Swedish screening programme was judged to be highly cost-effective in the contemporary setting in a publication by Wanhainen et al. from 2016[30], in which it was also estimated that every fourth patient who has an AAA detected through screening would have a longer life as a result of attending the screening programme. A very recent meta-analysis of the long-term results in the four randomized screening trials showed that screening reduces both all-cause mortality and AAA-related mortality[123].

Further research is required regarding potential psychological harm associated with detection of an AAA by screening. If the prevalence of AAAs continues to decline, follow-up of the cost-effectiveness of the screening programme is warranted.

Rupture

Intuitively, given the acute life-threatening character of ruptured abdominal aortic aneurysms, a rapid diagnosis in the emergency department would be of great importance. However, it is not always easy to make a correct diagnosis at the first assessment. Many physicians have encountered patients with rAAA who were initially misdiagnosed. The consequences of misdiagnosis of rAAA are largely unknown, and these were examined in **Study 2** and **Study 4** of this thesis.

Misdiagnosis

In **Study 2**, the consequences of misdiagnosis of rAAA patients who reach surgery were investigated and in **Study 4**, patients with rAAA who did not reach surgery were also identified. The main results of these studies were that misdiagnosis is common and affects more than a third of the patients who seek treatment for rAAA in an emergency department. Misdiagnosis was not only common, it was also associated with a substantially higher mortality in patients with rAAA. In the subset of patients who reached surgery, no significant difference in mortality or in the rate of complications could be detected. In adjusted analysis, misdiagnosis remained a significant risk factor for mortality in the whole patient cohort, but not in the subset of patients who reached surgery.

In both **Study 2** and **Study 4**, a lower proportion of the misdiagnosed patients had a first-recorded SBP of < 90 mmHg. Empirically and also according to previous reports[130-132], hypotension is a factor that is associated with an increased risk of dying in patients with rAAA. It would be expected that a cohort of patients where pronounced hypotension is less common would have a lower mortality than a cohort with a higher proportion of patients with pronounced hypotension. This was not the case in **Study 2**, where the misdiagnosed group with a lower proportion of hypotensive patients (12.8%) had a similar mortality to that of the correctly diagnosed group, in which 37.0% were hypotensive. It might be that the expected difference in mortality is counterbalanced by the misdiagnosis per se. It cannot be ruled out that the absence of any difference in mortality and complications between correctly diagnosed and misdiagnosed patients in **Study 2** can be explained by selection of more stable patients in the misdiagnosis group.

The frequency of misdiagnosis in **Study 2** (33%) and **Study 4** (38.9%) can be compared to that in previous heterogeneous studies, which found misdiagnosis rates of 25.6–68%[73,74,76-84]. The rate of misdiagnosis in **Study 2** and **Study 4** was slightly lower than the overall rate of 42% reported in a review and meta-analysis by Azhar et al. in 2014, but was higher than the 32% in the subset of studies after 1990 that were reported

in the same review.

For comparison, the frequency of misdiagnosis in the studies in this thesis was similar to or higher than those in previous reports on misdiagnosis in patients with aortic dissection (14.1–39%)[133-135]

The existing literature on how misdiagnosis affects outcome in rAAA patients is limited. To the best of my knowledge, four previous studies[74,76,77,79] have compared mortality in misdiagnosed patients and in correctly diagnosed patients. In two of these studies [76,77], statistical analyses of the differences were not done. Akkersdijk et al. (n = 38) and Marston et al. (n = 152) compared mortality in misdiagnosed patients and correctly diagnosed patients, and no significant difference was found. However, no adjusted analysis to account for confounders was done in these studies.

To the best of my knowledge, **Study 4** is the largest study to investigate how misdiagnosis affects outcome in rAAA patients, and the first to analyse outcome in multivariable logistic regression to account for potential confounders.

The high frequency of misdiagnosis and the associated higher mortality in misdiagnosed patients are important observations. Research in the field of vascular surgery is often focused on screening, methods and techniques at surgical intervention, and to some extent postoperative care. For instance, considerable resources have been used on randomized trials attempting to determine whether EVAR or open repair gives the best outcome in rAAA patients[95,97,136,137]. These studies have failed to demonstrate any clear benefit of either procedure. Investments are also being made worldwide in hybrid suites, in order to optimize the possibility of performing technically advanced endovascular procedures. Such investment may naturally have the potential to improve outcome in rAAA patients.

However, the observed frequency of misdiagnosis and the significantly worse outcome in misdiagnosed patients in **Study 4** tell us that the

importance of the basic clinical assessment in the emergency department must not be forgotten in this era of technical advancements in vascular surgery. A higher awareness of rAAA among emergency department staff and physicians is warranted, and further education about rAAA should be considered.

Open abdomen treatment after open repair

Leaving the abdomen open at the end of the procedure can eliminate the risk of development of abdominal compartment syndrome after open repair of an rAAA. Such a regimen would allow the possibility of avoiding the negative physiological effects of ACS, but might also increase the risk of complications such as infection and later abdominal hernia. Open abdomen treatment also requires resources for repeated redressing in an operating theatre. The rationale for **Study 3** was to use the fact that Sahlgrenska University Hospital had accumulated a sample of patients treated with open abdomen after open rAAA repair, which was large in this context (n = 79). In order to minimize confounding as much as possible, a control group was constructed by propensity score matching in Swedvasc, and to further adjust for possible confounders and increase the robustness of the analysis, a multivariable logistic regression analysis was done.

The main result of **Study 3** was that there was no difference in mortality or in the frequency of major complications between the groups, using either crude or adjusted analysis. There were slightly more graft infections in the group treated with open abdomen at Sahlgrenska University Hospital than in the controls, but this difference was not statistically significant.

The existing literature comparing treatment with a primary open abdomen and treatment with primary closure is very limited. A report by Acosta et al.[138] has indicated that initiation of open abdomen treatment at the primary operation might be of value in patients who are treated for aortic disease with open or endovascular surgery. However, patients

treated with open abdomen initiated at the primary operation in that study were compared with patients who needed a secondary decompressive laparotomy, which requires caution in interpreting the results since patients who need a secondary decompressive laparotomy might constitute a selection of patients with poor outcome. A similar comparison was made in a study by Sörelius et al.[116], where a subset of nine patients treated with open abdomen initially were compared with 21 patients who underwent a secondary laparotomy/decompression. No significant difference in mortality was observed between the groups. Rasmussen et al. compared mortality in patients treated with open abdomen at the primary operation or after a decompressive laparotomy—since it was difficult to close the abdomen—with patients who had the abdomen closed initially, and found a higher mortality in patients treated with open abdomen [139]. In the same study, no difference in mortality was seen when patients with open abdomen initially were compared with patients who needed a secondary decompressive laparotomy. Selection bias probably influenced the result in Rasmussen's study, since it is likely that patients in whom it is difficult to close the abdomen have a worse prognosis than patients in whom the fascia can be sutured without tension. In a small series reported by Oelsclager et al. (n = 23), no difference in mortality was seen between patients with primary closure of the abdomen and those with delayed closure[140].

An important limitation of **Study 3** was that 27% of the patients in the control group were treated with open abdomen (the treatment that the study was aimed to evaluate). A control group in which all the patients were treated with closed abdomen initially would obviously have been preferable. At the time of **Study 3**, it was not registered in Swedvasc whether or not patients were treated with open abdomen at the primary operation. Thus, this was found out after the propensity score matching was done and the medical records of the control group of patients were retrieved. We had expected that a small proportion of the patients in the control group would have been treated with a primary open abdomen. We did not foresee that treatment with a primary open abdomen would have been implemented to such a great extent (27%) in this subset of patients in Sweden. If primary open abdomen treatment were to be beneficial in

terms of mortality and complications, the 27% who were treated with open abdomen would dilute the result and possibly introduce type-2 error.

A randomized trial investigating whether primary open abdomen treatment or closure of the abdomen at the end of the primary procedure should be the treatment of choice after open repair for rAAA would be of great value. It is rather unlikely that such a study will ever be performed. In an era when EVAR is increasingly being used in rAAA patients, it would be demanding to arrange for a large enough sample in order to have sufficient power. Furthermore, surgeons would most probably be reluctant, and it would also be unethical to randomize patients where the abdomen cannot be closed without tension. This would exclude the selection of patients who are most likely to gain from primary open abdomen treatment.

Study 3 compared a cohort of patients who were all treated with open abdomen after open repair for rAAA, with a cohort who were treated with closed abdomen in the majority of cases (73%). Apart from this, the groups were very similar in terms of known and potential confounders. Given the fact that it is unlikely that a randomized controlled study attempting to answer the question will ever be performed, the meagre knowledge on the topic, and the limited existing literature, I consider that the findings in **Study 3** are important despite the fact that a minority of the patients in the control group were treated with a primary open abdomen.

The study did not show a survival advantage or a difference in the frequency of major complications in patients treated with a primary open abdomen rather than a primary closed abdomen after open repair for rAAA.

Conclusions

- The contemporary postoperative mortality was low in a national audit of patients with AAA detected by screening and age-matched controls.
- Patients with screening-detected AAAs had the same mortality and frequency of complications at 30 days as patients whose AAAs were not detected by screening.
- Misdiagnosis is common in patients seeking care for rAAA, and it is associated with a substantially increased mortality.
- No survival disadvantage or increased frequency of complications was observed in the subset of misdiagnosed rAAA patients who reached surgery.
- We did not find that treatment with a primary open abdomen after open repair for rAAA was associated with a lower mortality or with a lower frequency of major complications, relative to a control group in which the majority of patients were treated with primary closure of the abdomen. Our findings do not support a regimen of routinely leaving the abdomen open at the end of the procedure after open repair for rAAA.

Future perspective

Several areas in the field of AAA remain poorly investigated.

- It would be of value to investigate whether education regarding rAAA directed at emergency department staff and physicians would have the potential to reduce the frequency of misdiagnosis. A study comparing the frequency of misdiagnosis before and after a structured educational programme regarding rAAA, directed at emergency department staff and physicians, should be considered.
- A randomized controlled trial comparing primary closure of the abdomen in patients treated with open repair for rAAA would be desirable. Given the difficulties in performing such a study, it would be valuable to perform a cohort study comparing a group of patients to whom open abdomen treatment was given with a control group where all the patients had the abdomen closed.
- The possible psychological harm of being diagnosed with an AAA within a screening programme needs to be studied further.
- Further research investigating the reasons for the worse outcome of rAAA in women is warranted.
- Further research investigating the pathogenesis and aetiology of AAA, and possible ways of inhibiting the development or growth of an AAA, is clearly warranted.

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