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Treatment of abdominal and thoracic aortic aneurysms

Aspects on epidemiology and surgical outcome

KIM GUNNARSSON

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Abstract

Gunnarsson, K. 2021. Treatment of abdominal and thoracic aortic aneurysms. *Aspects on epidemiology and surgical outcome*. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1781. 76 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-1323-8.

Aortic Aneurysm (AA) is a life-threatening condition when ruptured (RAA), requiring immediate repair for survival. Since the 50´s, open repair, replacing the diseased vessel with a prosthetic (synthetic) graft, has been the gold standard. In the 90's, a new minimal invasive surgical technique, endovascular aneurysm repair (EVAR) was developed and has since become the dominant surgical method of choice in RAA treatment. The aim of this thesis is to assess trends in epidemiology, treatment and outcome of aortic aneurysms, with special focus on RAA.

Paper I is a population-based registry study of all surgical procedures performed for ruptured abdominal aortic aneurysm (RAAA) in Sweden 2008-2012. In this time period, some centres adhered to a distinct EVAR first strategy for treatment of RAAA, whilst others primarily performed open repair for RAAA. The analysis demonstrated no difference in mortality comparing centres with EVAR or open repair as primary treatment strategy.

Paper II is a nationwide population-based register study presenting the epidemiology of all RAAA in Sweden from 1994 to 2013. The study demonstrated a decreasing mortality in RAAA over time, due to the combination of a falling incidence, increasing hospital admissions and increasing proportion of patients undergoing surgical repair. The survival after surgical intervention improved over time, mainly due to the introduction of EVAR.

Paper III is a nationwide population-based register study to investigate long-term survival after ruptured abdominal aortic aneurysms (RAAA) repair in Sweden during twenty-four years (1994-2017). The study found that the long-term survival has improved over time, mainly explained by improved perioperative survival, despite that the operated patients generally became older and more fragile.

Paper IV is a nationwide population-based register study covering the time period 1997 to 2017, assessing the epidemiology of operated intact and ruptured descending thoracic aortic aneurysms (dTAA and RdTAA) in Sweden. This analysis shows increased incidence of intact dTAA repair due to broad introduction of thoracic EVAR (TEVAR). Early postoperative mortality decreased, despite an increasing proportion of those undergoing repair being ≥80 years and with more comorbidities. No changes on incidence or mortality was detected among RdTAA repairs.

In conclusion, modern treatment of aortic disease with endovascular techniques has resulted in a significant change in practice for treatment of RAA, and dTAA. The above-mentioned nationwide population-based register studies indicate that EVAR/TEVAR have resulted in improved survival of patients suffering from RAAA and the results after dTAA repair have improved.

Keywords: Aortic aneurysm. Ruptured aortic aneurysm, Endovascular aneurysm repair, Open aortic repair, Aneurysm, Outcome

Kim Gunnarsson, Department of Surgical Sciences, Vascular Surgery, Akademiska sjukhuset ing 70 1 tr, Uppsala University, SE-751 85 Uppsala, Sweden. Centre for Research and Development, Gävleborg, Region Gävleborg, Uppsala University, SE-80188 Gävle, Sweden.

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To Elin, Johannes, Nike and Ingrid

List of Papers

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

I Gunnarsson, K., Wanhainen, A., Djavani Gidlund, K., Björck, M., Mani, K. (2016) Endovascular Versus Open Repair as Primary Strategy for Ruptured Abdominal Aortic Aneurysm: A National Population-based Study. *European journal of vascular and endovascular surgery, 51(1):22-8.*

II Gunnarsson, K., Wanhainen, A., Björck, M., Djavani Gidlund, K., Mani, K. (2021) Nationwide Study of Ruptured Abdominal Aortic Aneurysms during Twenty Years (1994-2013). *Annals of Surgery, 274(2):e160-e166.*

III D'Oria, M*., Gunnarsson, K*., Wanhainen, A., Mani, K. (2021) Long-term Survival after Repair of Ruptured Abdominal Aortic Aneurysms is Improving Over Time - Nationwide Analysis During Twenty-four Years in Sweden (1994-2017). *Annals of Surgery, doi:10.1097/SLA.0000000000005030. Online ahead of print.*

*Mario D'Oria and Kim Gunnarsson contributed equally to this work and share first authorship.

IV Gunnarsson, K., Wanhainen, A., Mani, K. (2021) Treatment of descending thoracic aortic aneurysms in Sweden (1997-2017). *Manuscript.*

Contents

Abbreviations

AA	Aortic Aneurysm
AAA	Abdominal Aortic Aneurysm
CDR	The Cause of Death Registry
CI	Confidence Interval
CT	Computed Tomography
dTAA	descending Thoracic Aortic Aneurysm
EVAR	Endovascular Aortic aneurysm Repair
ESVS	The European Society for Vascular Surgery
HR	Hazard Ratio
ICD	International Statistical Classification of Diseases
MRI	Magnetic resonance imaging
NPR	The National Patient Registry
NCSP	NOMESCO Classification of Surgical Procedures
OSR	Open Surgical Repair
pEVARc	Primary Endovascular Aortic Repair Centre
PIN	Personal Identity Number
pORc	Primary Open Repair Centre
QR	Quality Register
RCT	Randomized Controlled Trial
RAAA	Ruptured Abdominal Aortic Aneurysm
RdTAA	Ruptured descending Thoracic Aortic Aneurysm
Swedvasc	The Swedish Vascular Registry

SPSS	Statistical Package for the Social Sciences
TAA	Thoracic Aortic Aneurysm
TAAA	Thoracoabdominal Aortic Aneurysm
TEVAR	Thoracic Endovascular Aortic aneurysm Repair

Introduction

An aortic aneurysm is a silent disease that frequently does not cause the individual affected by it any harm or pain, until the day it ruptures. Suddenly, the immediate chance of survival is between 10-20%. If the patient with an aortic rupture is fortunate enough to reach a hospital alive, which approximately 50% of all ruptures do [1], the chance of survival increases to 40-50%. For patients undergoing surgery, chance of survival is 60-70% [2-4].

Aortic aneurysm is a widening (dilatation) of the aorta due to pathological weakening of the aortic wall. The majority of AA are localized in the infrarenal abdominal aorta (AAA), whilst some are located in the thoracic aorta (TAA) or other aortic locations such as the aortic arch or paravisceral aorta. The pathophysiological mechanisms causing AA are multifactorial, and not entirely known. Risk factors associated with AA include male gender, age, smoking, heredity, genetic disorders and presence of cardiovascular disease. There are several definitions of AA. Common definitions are >50% increase in aortic diameter compared to the adjacent proximal aortic segment, or 50% larger diameter of the aorta than the expected [5, 6]. The clinically useful definition for AA however is a maximum aortic diameter of 30 mm (particularly for the infrarenal aorta) or more [7, 8]. The shape of the aneurysms may be fusiform, saccular or multi-lobular.

This thesis assesses the epidemiology, treatment and outcome of aortic aneurysms in Sweden, with special focus on ruptures, in the context of changing surgical technique.

Background

History of aortic surgery

The term “ruptured aortic aneurysm” originates from Greek and Latin. Rupture originates from the Latin rupture, "the breaking" from past participle stem of rumpere "to break”. The term aorta originates from the ancient Greek word “ἀορτή” aorte and derives from the verb “ἀορτέω” aorteo and means “to be hung up” or “to raise”. The word aneurysm is from the Greek “ανευρυσμα” aneurysma which has the meaning, “a widening/an opening” [9, 10]. The first description of aneurysms is in The Ebers Papyrus [11], dating back to around 2000 BC. In these scrolls the first recommendation regarding aneurysmal treatment is described.

Antyllus [12], a Greek surgeon of the 2nd century AD, left the earliest record of therapy for aneurysms. After that a few advances were made on the surgical approach to aneurysms, but Vesalius (1514-1564), a Belgian anatomist and physician, was the first who described aortic aneurysms in 1554 [13]. The following 400 years was followed with numerous aneurismal treatment techniques based on different ligation strategies. It was not until Matas (1860-1957) ligated an AA successfully in 1923 that it was considered possible to treat AA. Matas had earlier developed endoaneurysmoraphy (1888) as a treatment for aneurysms in general. Other experimental operative techniques followed such as needling, wiring, proximal banding, cellophane wrapping (used to operate on Albert Einstein) and electrocoagulation [14]. In 1951, the first successful reconstructive AAA repair were performed by Dubost [15], using an aortic homograft. One month prior to Dubost’s success, Freeman and Leeds [16] restored arterial continuity with an iliac vein as a graft but this patient died 6 hours after surgery. Later that year, Freeman operated three more patients applying the same technique, with good results in one of them.

In 1953 Bahnson [17] was credited for the first successful ruptured AAA (RAAA) repair. The poor availability of aortic homograft fuelled the development of synthetic aortic substitute starting with Vinyon-N cloth (1952) [18], Teflon and later, still today used, Dacron in1958 [19].

Before entering the modern era of AA and RAA treatment a short comment on diagnosis must be made. In 1895, Roentgen discovered the X-ray that would become one of the cornerstones of the diagnostics of AA, leading to the modern CT-scan. The other is the development of ultrasound in the 1950´s [20].

These two discoveries are what today define modern aneurysm diagnostics, morphological assessment and basis for surgical intervention strategies.

In the 1980s, Volodos had an idea of less invasive approach to treat AA and started with different innovative experiments, developing catheter-based approaches to treat aortic aneurysms. In 1986 he could use a hybrid approach to AA repair for the first time [21]. This new technique didn't reach worldwide recognition until Parodi [22] in 1991, published his paper "Trans femoral intraluminal graft implantation for abdominal aortic aneurysms".

In 1994, endovascular repair of a ruptured abdominal aneurysm was first performed in Nottingham, UK [23] and for ruptured thoracic aneurysm described by Semba et al in 1997 [24].

Aneurysm histology and pathology

The aortic wall is basically composed of three different layers. An inner layer (tunica intima), that has a surface of endothelial cells, attached to the basement membrane and are in direct contact with the blood. A middle layer (tunica media), containing elastin, collagen and smooth muscle cells. The third and last layer (tunica adventitia), is the outer layer containing a structure of collagen, fibroblasts and the aortic wall`s own blood vessels, vasa vasorum.

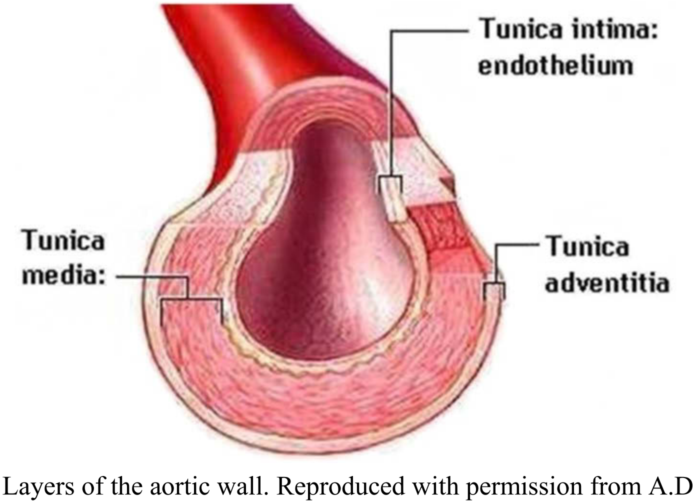

Figure 1. Layers of the aortic wall. Reproduced with permission from A.D.A.M.images© 2021 Ebix, Inc.www.adamimages.com.

The aortic wall weakens during the formation of an aneurysm. This occurs mainly because of a degradation of the connective tissue due to an increased proteolytic activity of matrix metalloproteinases, responsible for the degeneration of elastic lamellae and extracellular matrix proteins. A chronic inflammation leads to the infiltration of macrophages, neutrophils, mast cells and lymphocytes [25, 26] affecting the media and adventitia. This leads to a disturbance in the normal balance between tissue inhibitor metalloproteinase and matrix metalloproteinase favouring an enhanced matrix degradation and loss of mechanical strength.

The pathogenesis in AAA and dTAA differs in that way that, AAA is more related to atherosclerotic process while TAA has a large genetic component. People with TAAs have a family history of aortic disease in 20-25% in form of Marfan, Vascular Ehlers- Danlos, Loeys- Dietz Syndrome ore other types of genetic disorders [27].

The underlying mechanisms for developing AA is very complex and still not fully understood.

Epidemiology

Prevalence

AAA

An autopsy study from 1992 [28] with an autopsy rate of 85% concluded that 4.3% among men and 2.1% among women in Malmö, Sweden had an abdominal aortic aneurysm. Since then, the autopsy rate has declined in Sweden and was in 2017 only 7% [29]. Other studies, based on ultrasound screening programs during the 1980s and 1990s found the prevalence to be 4-7.6% in men and 1% among women [30-32]. The prevalence of AAA increases with age and has a strong association with increasing years of smoking and cigarettes smoked [33]. Recent studies based on screening on 65-year old men, indicate a decreasing prevalence in AAA reporting a prevalence of 1.3% in the UK and 1.5% in Sweden 2014 [25, 34, 35]. Contemporary reports among women of the same age and area, display a prevalence of 0.43% and among women 70-75-years of age 0.5-1.1% [36, 37]. The decreasing prevalence of AAA in men is explained mainly as a result of reduced smoking [38] and treatment of other cardiovascular risk factors and lifestyle changes [39].

dTAA

The knowledge/data on the prevalence of dTAA are scarce, not up to date and heavily burdened by selection and publication bias. It requires imaging in form of CT or Magnetic resonance imaging (MRI) to detect dTAA. Existing literature reports a prevalence of dTAA to 3.5-10.4/100,000 person-years [40-42] and a imaging study from Japan on subjects between 50-70 years of age, found a prevalence of 0.06% [43].

Incidence of aortic rupture

Ruptured Abdominal Aortic Aneurysm (RAAA)

Most studies on RAAA incidence are based on autopsy reports or mortality statistics [2, 44, 45] or studies of small aneurysms in a prospective setting [46, 47]. These studies demonstrated an increase in RAAA incidence over time with an incidence between 14.7-21.3/100,000 person-years [2, 45, 48]. Contemporary reports however, indicate a decrease in rupture incidence to 4.0-12.8/100,000 person-years [3, 49-51], mainly explained by decreasing prevalence of AAA. Some 12.6-18.0 % of all RAAA occur in men below the age of 65 [44, 51-53]. Mean patient age at the time of rupture is typically 75-79 years [54-57] and approximately 75% of all ruptures occur in men.

The decreasing prevalence of AAA in some countries also reflects a declining incidence of rupture [50, 58]. However, an increase in burden of aortic aneurysm disease has been reported in some countries and global areas. The variations are not only in mortality but also in the incidence of RAAA [59, 60]. Very few contemporary reports include ruptures that do not undergo surgical treatment, i.e. ruptures that are never admitted to any healthcare facility or not undergo surgery after hospital admission.

Ruptured descending thoracic aortic aneurysm (RdTAA)

Studies on RdTAA incidence are, like studies on the prevalence of dTAA, scarce. An RdTAA incidence of 2.5/100,000 person-years has been reported [4]. Other reports have concluded that the incidence of thoracic aortic disease and the surgical activity of RdTAA is increasing [61, 62] in contrast to AAA incidence [63]. Mean patient age at the time of ruptured dTAA is somewhat lower compared to RAAA at 71-74 years [62, 64]. The gender distribution in RdTAA is also different and is more even (1-1.7:1; Male:Female ratio) [41, 62, 64].

Natural course of AA and risk of rupture

AAA

An aortic aneurysm, no matter where it is located, has the tendency to gradually expand over time. How much and how fast an aneurysm will grow varies between individuals. Mean expansion rate has been estimated to 2-3 mm per year [65] but generally, larger aneurysms grow faster with an estimated expan-

sion of 5-10% per year [66, 67]. The most significant factor associated with increased growth rate is smoking, while presence of diabetes is associated with slower growth rate [67]. Several clinical trials with drug therapy have been carried out without being able to prove any effect on expansion rate despite past associations and observational studies. Recently, it is hypothesized that the reduced risk of AAA expansion in diabetic patients may be an effect of metformin treatment [68-70] in many diabetics; thus studies are under way to evaluate the effect of metformin on AAA growth rate among non-diabetic AAA patients [71]. Hypertension, female gender and continued smoking have been associated to an increased risk of rupture. In a prospective study among patients with AAA of 40-55 mm, risk of rupture was four times higher among women than among men [47]. The mean size of the aneurysm at rupture has been reported to be 7 to 8 cm [56, 72] and the risk of rupture increases with aneurysm size. While most ruptures occur in large AAAs, small aneurysms may also rupture. The mean risk of rupture of aneurysms of 3.0-5.5 cm in diameter is estimated at 1.0-1.6% per year [73, 74] and in Finland, 5.6% of all ruptures in men and 11.5% of ruptures among women occurred in those having an AAA diameter below 5.5 cm [52].
Other factor to take in consideration to estimate rupture risk are aneurysm morphology and growth rate.

Table 1. *The estimated rupture risk per year in %, based on aneurysm diameter.*

Diameter, mm	Rupture risk %, per year	Data source
30-55 mm	1.6 %	Powell JT et al [74]
55-59 mm	3.5 %	Parkinson, F [75]
60-70 mm	10-20 %	Lederle FA et al [76]
70-80 mm	30-40 %	Lederle FA et al [76]
>80 mm	30-50 %	Lederle FA et al [76]

dTAA

The expansion rate of dTAA and the associated factors are largely shared with the natural course of AAA and that larger diameters AA tend to expand faster [77-79]. Depunt et al followed 67 dTAA patients with CT-scans every 6-months until they fulfilled the indications for operative treatment and found that except for history of smoking, hypertension (elevated diastolic blood pressure) particularly was associated with dTAA growth [80]. Female sex also tends to have an elevated risk of rupture [81]. The diameter of the dTAA is the risk factor that most clearly predicts the risk of yearly rupture according to ESVS guidelines on management of dTAA [82]. The rupture risk is estimated at 15% at diameter >60 mm and approaches 50% when it reaches >70 mm in diameter [77, 83, 84].

Aortic aneurysm repair

Management of ruptured AA

Ruptured aortic aneurysm is a deadly condition with a reported overall mortality 80-97% depending on where the aneurysm is located [4, 73]. Data indicates that RAA is the cause of death in nearly 1% of the male population >60 years of age in Sweden[85]. A major concern is that roughly half of the patients with RAAA die outside the hospital prior to reaching medical care [2-4, 86]. Similar data regarding RdTAA are not readily available. Symptoms of RAA are chest, abdominal or back pain not rarely in combination, palpable pulsatile abdominal mass (in case of abdominal aortic aneurysm rupture) and hypotension. Ultrasound can be useful to diagnose RAAA in the emergency room but CT angiography is the most accurate diagnostic method to assess presence of aortic rupture regardless of location [87]. CT will also give guidance for what type of surgical approach each patient will be suitable for and is an invaluable tool in the preparation of surgery. After diagnosis is made the recommendation is permissive hypotension for patients with RAA [82, 87].

Among all patients who reach hospital, the rate for surgery are reported at 20-87% where RdTAA-rate is in the lower end [3, 55, 62, 86]. The classic way to operate a RAA is open surgical repair but as minimal invasive endovascular repair have been developed as a method of choice, endovascular repair has become increasingly used [1, 88-90].

Open Surgical Repair

Open surgical repair (OSR) of an AA is a surgical procedure associated with a high risk of mortality and morbidity due to its stress on the patient from blood loss and aortic clamping. It has traditionally been the only operation available 24/7 for ruptures at most hospitals. The patient is operated under general anaesthesia. Depending on which part of the aorta needs to be exposed, the aorta will be accessible via a long midline, rooftop incision (with or without a retroperitoneal approach) or a thoracotomy, with a cross-clamping of the neck of the RAA and the iliac arteries. The aneurysm sac is thereafter opened up and a graft is sutured to replace the aneurysm. The complexity of the operation varies with the location of the rupture, and with this also the risk of complications varies.

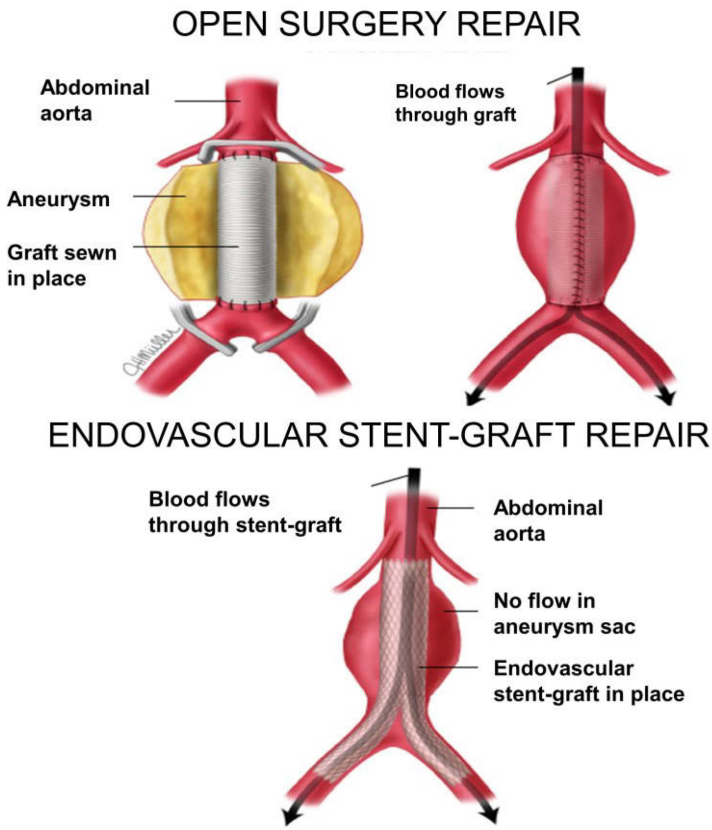

Figure 2. Open and endovascular repair. Reproduced with permission from: Dalman RL, Mell M. Overview of abdominal aortic aneurysm. © 2018UpToDate, Inc. www.uptodate.com.

Endovascular aneurysm repair

Endovascular aortic repair (EVAR) is today the method of choice for treatment of intact AAA in many countries and is the surgical method in 5-40% of the treated RAAA cases in an international comparison [72]. The most recent guideline from the European Society for Vascular Surgery (ESVS) 2019, on management of RAAA stated "In patients with ruptured abdominal aortic aneurysm and suitable anatomy, endovascular repair is recommended as a first option" [87]. In Sweden, >60% of all RAAAs underwent surgery with EVAR in 2020 [91]. The use of EVAR for RAAA not only varies among countries, but there are major differences between regions in different countries [3, 55, 56]. For treatment of dTAA and RdTAA, thoracic endovascular aortic repair (TEVAR) has during last decade become more and more dominant as the surgical method of choice with reported share of 36-90% [62, 90, 92].

An endovascular procedure is, in comparison to OSR, a minimally invasive operation where the patient is operated preferably under local anaesthesia. The aorta will be accessible via a percutaneous puncture in the femoral arteries which reduces the hemodynamic effect and the risk of perioperative blood loss. With guidance of fluoroscope, a stent graft is deployed into the aorta to exclude the aneurysm from blood flow and seal the rupture in acute cases. The puncture site is thereafter closed with a percutaneous closure device or open cut-down with sealing sutures to the femoral arteries, leaving 1-5 cm long incision in each groin.

EVAR and TEVAR require an aortic morphology suitable for endovascular repair and also measurements to determine the correct size of the stent grafts. Therefore, a preoperative CT-aortography is mandatory in order to perform an endovascular procedure. The procedure also requires an operating theatre with the ability to use a fluoroscope, and surgeons or interventionists used to the technique.

Incomplete sealing results in early or late endoleaks, which may result in surgical failure and death due to haemorrhage. Due to the fact that endoleaks may occur over time after EVAR/TEVAR, long-term imaging follow-up after the procedure is required [82, 87, 93, 94].

Surgical Outcomes

RAAA

A meta-analysis of 50 years of RAAA repair (publications 1955-2000) displayed an overall postoperative mortality rate of 48% and a reduction in early mortality after surgery for rupture with 3.5% per decade[95]. In more recent studies, overall mortality rate after RAAA surgery varies between 28-35% [51, 56, 72, 96, 97] in mixed settings of EVAR and OSR, suggesting that an increased use of EVAR improves 30-day mortality rate. Several observations and registry studies support this and report an early mortality rate of 7-24% after EVAR procedure for rupture [55, 56, 72, 98], but one must keep in mind, all RAAAs do not have a suitable morphology to be operated with EVAR so selection bias often occurs. The theory is that EVAR reduces the operative trauma, reduces blood loss, avoids cross clamping of the aorta and reduces the ischemic time of the lower body.

Based on the four randomised controlled trials that have been conducted, the Cochrane Library concluded that the short-term survival did not differ between EVAR and OSR [99], Table 2. The results from the most contemporary RCT´s, however, verified improved 3-year survival after EVAR compared to open repair [100]. The current European Society for Vascular Surgery guideline recommends EVAR as primary strategy for treatment of ruptures if anatomically suitable [101]. However, provision of around the clock EVAR services for treatment of RAAA requires both access to adequate technology (fluoroscopy, hybrid operating theatre, stent graft stocks), as well as endovascular know-how among on call surgical/interventional staff. Therefore, many hospitals still rely on open repair as the primary technique for treatment of ruptures during on call hours.

Table 2. *30-day mortality in the RCT´s (randomized controlled trials) and Study I (strategy mortality), which compares OSR with EVAR of RAAA.*

Trials	Study Period	Country	N of patients	30 day mortality		1 year mortality	
				EVAR	**OSR**	**EVAR**	**OSR**
Improve 2014 [96, 102]	2009-2013	UK	613	35%	31%	41%	44%
AJAX 2013 [97]	2004-2011	Netherlands	116	21%	25%	Na	Na
ECAR 2015 [103]	2008-2013	France	107	20%	24%	30%	35%
Hinchliffe 2006 [104]	2002-2004	UK	32	53%	53%	Na	Na
Gunnarsson 2016 [56]	2008-2012	Sweden	1304	28%	27%	40%	35%

N= number, Na= not available

Complications after RAAA repair include cardiac events, renal failure and respiratory failure, complications that are associated with all major surgery with a risk of massive bleeding and circulatory effects. More specifically linked complications to RAAA are abdominal compartment syndrome (ACS) and bowel ischemia. ACS is a condition with intra-abdominal hypertension that causes organ dysfunction or failure, occurring in 3.5-7.5% of all RAAA repair [105, 106]. Bowel ischemia is the result of impaired circulation, affecting the layers of the colon wall and occurs after RAAA repair in 15-36% of the cases [107, 108]. All of the above mentioned complications contribute to increased mortality after RAAA repair

RdTAA

Reports after RdTAA surgery in the 80´s displayed a mortality rate of 97-100% [4]. More contemporary data indicate a mortality rate (in-hospital or within 90-days) of 24-50% and a mid-term mortality (1-2 years) closely to 50% in mixed settings of TEVAR and OSR. The same trend as in the treatment of RAAA is seen, that endovascular surgery may improve short-term mortality [62, 90, 109-113]. The most recent data reports 30-day- and 1-year mortality to 16.5% and 25.3% respectively [114]. All studies on outcome are observational or registry studies, no randomised controlled trial on RdTAA has been performed.

Indications for repair on intact dTAA is set for a diameter of 60 mm or larger according to the ESVS guidelines on management of dTAA [82]. This recommendation is based on that the 60 mm aneurysms carries an annual risk of rupture of 10% and mortality rates in elective OSR cases reports to 8-13% (in hospital mortality) [115]. No studies comparing OSR with TEVAR in an elective setting is yet existing [116], but a systematic review and meta-analysis concluded that TEVAR was associated with lower 30-day mortality (OR, 0.6; 95% CI, 0.36-0.99) after intact dTAA surgery [111]. The most recent data on intact dTAA operated with TEVAR display an early mortality (in hospital or 30-days) rate of 5.0% [62, 112].

The rapid development of TEVAR during the last decade to become the dominant treatment of RdTAA is most likely due to the fact that RdTAA is operated at highly specialized vascular centres, with extensive experience in operating intact dTAA, where it´s possible to offer endovascular solutions around the clock and therefore been easier to implement.

Feared complications after RdTAA repair are paraplegia and stroke, but also cardiac events, renal failure and respiratory failure.

Registries

"I am considered eccentric because I say publicly, that if hospitals want to be sure of getting better, they have to find out what results they have. They have to analyse their results to find strengths and weaknesses. They have to compare their results with others. Such views will not be eccentric in a few years".
-*"End Result Idea"* Ernest Amory Codman, 1917

The idea of a hospital register, to help physicians monitor and improve the quality of care delivered, was first presented by the British physician Sir Thomas Percival (1740-1804) in 1803 [117].

Ernest Amory Codman (1869-1940) was a surgeon at Massachusetts General Hospital, member of the Harvard medical faculty in Boston, USA and is considered to be one of the pioneers in evidence-based medicine. Dr Codman used "End Result Cards", containing demographic data, diagnosis, the treatment the patient received as well as outcome. Each patient had one year follow-up. With the knowledge he gained from his work he created the "End Result System" leading to the publication of the *"End Result Idea"* in 1917. In early 1920, Codman established a bone tumour registry considered to be the first quality register (QR) in the world [118-120].

Swedish national registries

The first document recorded that can be called a registration of a Swedish local population is dated back to 1620. This was done by the Church of Västerås to keep track of conscripts and population census. The "Church act of 1686" laid the foundation for population statistics, which stated that the Swedish church was required to keep parish registers in an organized manner [121, 122]. This was the start of a long tradition of registering Swedish citizens. In 1749 the so-called "Tabellverket" was introduced, a nationwide reporting system for population statistics in Sweden and was published for the first time in 1764, making it to the oldest ongoing population register in the world.

In 1947, a decision was made that all Swedish citizens should have a personal unique identification number (PIN) with one of the goals being able to link together the many different registers that were now, or in the future, established [123]. In 1975, the first Swedish QR (Swedish Knee Arthroplasty Register) was established by Professor Göran Bauer in Lund, inspired by Harvard University after Prof Bauer had worked there for a few years. This was the start for surgical quality registers in Sweden. Currently, there are 107 different health care QRs in Sweden that provide great opportunities to perform unique registry-based research with national coverage and possibility to inter-link registries using the unique identification number [124, 125].

The studies in this thesis are based on patients identified from three national registries linked by the unique identification number.

Validation of register

Validity: Indicates the extent to which data and findings are true for the studied population.

Using register data in research has always been debated due to registers' validity and completeness. For data to be valid, high data quality is required. High quality data is relevant, complete, accurate and consistent. To ensure the quality of the data in registers, they should go through a validation process that includes an internal and external validation. The result of such validations should preferably be made publicly available.

Internal validation: refers to a validation of the data fields recorded in a register, pertinent to a specific individual/patient, and their completeness as well as accurateness. This is usually done by controlling the register data against source data (medical records) but also against an alternate source of data, for example the national patient register.

External validation: Is a validation of coverage rate of the intended population that is in the register. As an example, the external validation respond to the question: Are all the treated patients eligible for inclusion in the current registry actually included? An independent source of data is used in the validation process to estimate the degree the specific cases in question are registered, and evaluate if data missingness is systemic (affected by bias) or random.

The purpose of these validations is to secure that data from QRs represent as true a picture of the real world as possible, so that results from observational studies (with data from a validated QR) can be recognized as true. Preferably, a registry validation should be performed by independent and competent validators[126].

The Swedish vascular registry

The Swedish vascular registry (Swedvasc) was initiated in 1987, originally started as Vascular Registry in Southern Sweden (VRISS), and is a prospective vascular surgical quality registry. It is the second established surgical quality registry in Sweden [127, 128]. The Swedvasc reached national coverage by 1994 and during the past 30 years, Swedvasc has offered a unique opportunity for registry-based research on vascular surgery and generated over 100 scientific publications and several dissertations.

The registry includes data on open surgical and endovascular procedures performed on peripheral arteries and veins at participating vascular centres. Swedvasc is validated internally and externally with >90% coverage for AAA repairs performed in Sweden. Data on short- and long-term survival after repairs is incorporated into the registry through automatic cross-linkage with the population registry [129, 130], resulting in 100% accurate mortality data for patients with the Swedish unique personal identifier number. In 2020, almost 20,000 procedures were registered in the Swedvasc registry. The registry produces an annual report, based on figures submitted by individual vascular centres throughout Sweden evaluating the performance of the centres, and these are published openly since 1997. Ongoing projects are published under Research on Swedvasc website at http://www.ucr.uu.se/swedvasc/forskning/pagende-projekt.

The National Patient Registry

In 1964, the Swedish National Board of Health and Welfare (NBHW) started to collect data regarding in-patients at public hospitals. That was the beginning of The National Patient Registry (NPR) that received full national coverage 1987, due to mandatory participation for all county councils [131].

The registry today, contains patient data on all out-patient and in-patient health care contacts, including data on gender, age, place of residence, hospital/clinic, date of admission and discharge, length of stay, admitted from, discharged to, as well as diagnosis and procedure codes. Yearly coverage level comparisons against different Swedish quality registers are made together with validation loss of, among other things, main diagnosis and invalid PIN. In 2020, the coverage was approximately 99% of all inpatient hospitalisations and visits [132].

The Cause of Death Registry

The Swedish cause of death registry (CDR) is one of the oldest such registries in the world, dating back to 1749. In 1860 it became mandatory that the death certificates were issued by a medical doctor in communities that had access to one and the modern version was established in 1911.

The CDR is managed by NBHW and contains the official statistics on all contributing causes resulting in death, as well as time of death. All persons who at the time of death were registered in Sweden, regardless of whether the death occurred within or outside the country are included in the register. Persons who have died during a temporary stay in Sweden, asylum seekers who have not yet received a residence permit and emigrated Swedes who are no longer registered in Sweden are not included in the register. CDR provides the basis for the official statistics on the causes of death in Sweden. The statistics is based on the cause of death certificates, issued by a medical doctor, and has a loss of approximately 0.8% [133]. This applies, for example, to deaths abroad or deaths where the deceased has been found after a long period of time and the cause of death can no longer be determined. In addition, there are insufficiently specified causes of death, which are estimated at 2.7% [133] and the definition of which is determined by the World Health Organization. The registry's data is also used for descriptions of the population's health, as a basis for efforts in health care and for research. The cause of death statistics is internationally comparable for those countries affiliated to the World Health Organization and thus committed to complying with definitions and instructions in the International Statistical Classification of Diseases and Related Health Problems (ICD) [133].

Rationale

The endovascular revolution has drastically changed the landscape in management of AA. This is especially true for ruptured AA, which is a severe condition that requires immediate surgery for the person affected to be able to survive. Minimally invasive options for treatment of thoracic aortic disease have also resulted in changes in patient selection, and data suggest that epidemiology of thoracic aortic disease and its management is changing in modern times. Whilst the effect of endovascular treatment on outcome of RAA has been assessed in RCTs evaluating patients treated with open repair or EVAR, the overall effect of modern management of patients with aortic rupture on epidemiology of disease and outcome is less well studied.

Sweden with its vascular surgical quality registry and access to population-based data from a population of 10 million people opens up a unique opportunities to study epidemiological developments of disease prevalence and outcome on a national level. The current thesis thus builds on this opportunity to update on national incidence and treatment outcome of RAA and TAA to reflect “real world” setting.

Aims of the thesis

The overall aim of this thesis was to assess trends in epidemiology, treatment and outcome of ruptured abdominal aortic aneurysm and thoracic aortic aneurysms in Sweden, in the context of changing surgical technique. The specific aims were:

1. To investigate if a primary EVAR-strategy for treatment of aortic rupture achieves a better peri-operative outcome after RAAA surgery compared to open repair (Paper I)

2. To analyse trends in the epidemiology of RAAA in Sweden and assess surgical treatment rate and outcome in the context of changing prevalence of AAA and evolving surgical techniques (Paper II)

3. To assess Long-Term survival after RAAA repair in Sweden and evaluate changes in survival outcome over time (Paper III)

4. To assess trends in the epidemiology of intact and ruptured descending thoracic aortic aneurysms repairs, as well as the effect of the increasing use of TEVAR on surgical treatment rate and outcome (Paper IV)

Patients and methods

The observational studies in this thesis are all based on patients identified from CDR, NPR or Swedvasc. The patients included in study I-III are >50 years of age. In study IV, all ages were included. All registries and databases are linked by the PIN number every Swedish residents obtains; therefore, non-residents without a PIN were excluded from the studies.

Table 3. *Overview of the study design in the thesis.*

Study	Design	Period	Patients (n)	Source	Date of data extraction
I	Population-based registry study	2008-2012	Operated RAAA (1 304)	Swedvasc	May 2014
II	Nationwide Population-based registry study	1994-2013	All RAAA (18 762)	Swedvasc NPR CDR	May 2015
III	Nationwide Population-based registry study	1994-2017	Operated RAAA (8 928)	Swedvasc NPR CDR	September 2019
IV	Nationwide population-based registry study	1997-2017	Operated dTAA, intact and ruptured (875)	NPR CDR	March 2020

RAAA= ruptured abdominal aortic aneurysm, dTAA= descending thoracic aortic aneurysm, NPR= the national patient registry, CDR= the cause of death registry

Study I

This study, which aimed to evaluate EVAR as primary strategy for treatment of RAAA, included all patients who were operated on in Sweden from May 2008 to December 2012 as registered in the Swedvasc registry. In total 1,304 patient were included from 29 vascular centres; hospitals with no elective aortic surgery were excluded. Preoperative data and peri-operative results were compared for hospitals operating >50% of their ruptures with EVAR, referred to as primary EVAR centres (pEVARc), versus those with <50% EVAR, primary open repair centres (pORc). Three centres qualified to be pEVARc, all of them referral centres. The assumption was thus made that if a hospital uses EVAR on >50% of their RAAA cases, EVAR is considered to be their primary choice of method. Patient characteristics and comorbidities were compared between the groups.

The primary outcome for the analysis was peri-operative survival (within 30-days), with secondary analysis of mid-term (1 and 2 years) survival after surgery. Subgroup analyses included assessment of outcome among referrals, (i.e. the patient is diagnosed at a local vascular centre but operated on at a referral centre covering that area) and octogenarians. Predictors of peri-operative mortality were assessed.

Statistics

For comparison of mean values with normally distributed data, independent samples t-test was used. For rates and 30-day mortality, Chi-square was used. Differences in midterm mortality were tested with the log-rank test and estimated with Kaplan-Meier analysis. To estimate predictors of peri-operative mortality, uni- and multivariable binary logistic regression with forced entry was used. Statistical significance was defined as P values <0.05, all tests were two-sided. Data management and statistical analysis were performed with SPSS statistics version 22 (IBM, Armonk, NY, USA).

Study II

The intention with the study was to capture all patients affected by RAAA during 20 years, (1994 to 2013) in order to make an updated assessment of the RAAA epidemiology and result after treatment in the light of a more modern management of AAA with the impact of increasing use of EVAR. All patients in Sweden who have been cared for, operated on, been in contact with healthcare or have died, with the diagnosis RAAA, were identified from CDR, NPR and Swedvasc, merged into one database by PIN. ICD and NOMESCO Classification of Surgical Procedures (NCSP) codes were used to define operated and not operated patients.

The study period was divided into four 5-year groups for analysis to assess changes in characteristics, surgical activity and mortality over time. Approximately 3/4 of RAAA patients was men, therefor men and women were separated in the analysis to assess sex-specific outcome. The cohort was also divided into 2 age groups, 50-79 and >80 years of age, to assess outcome in these two subgroups.

The primary outcomes of the study were the RAAA incidence and mortality (≤ 90-days after rupture), secondary outcome were proportion of RAAA presenting to hospital, how many of those were operated on and surgical outcome.

Statistics

Data management and statistical analysis were performed with SPSS statistics version 25 (IBM, Armonk, NY, USA). Patients characteristics were evaluated with Chi-square and ANOVA for categorized and continuous variables, presented in 5-year periods with Bonferroni corrected P-values.
Trends in incidence, patients presenting to hospital and mortality over time (presented per 100.000 person-year) were evaluated with linear regression. Proportions of patients admitted to hospital, operated on, surgical turn-down rates, surgical mortality rates and overall mortality rates were assessed per 5-year period and evaluated with age-adjusted Poisson regression. All tests were two-sided and significance was set at <0.05.

Study III

This nationwide analysis of the long-term survival after RAAA repair was based on all patients who had undergone surgery due to RAAA identified from the NPR and Swedvasc. The study is a continuation of study II but with the focus exclusively on those surgically treated for RAAA in the light of shifting surgical strategies from OSR to EVAR. In addition this study has an updated data extraction to extend over a longer period of time, 24 years (1994-2017), and to cover previous contacts with healthcare to evaluate comorbidity. NCSP codes were used to define type of surgical approach (EVAR or OSR). The study period was divided into three 8-year periods for analysis to assess changes in survival over time and stratification of the cohort was done into surgical strategy and octogenarians vs non- octogenarians.

Crude long-term (5-year) survival were primary endpoint. Relative long-term survival after excluding early deaths (<90-days) in comparison with a matched (sex, age, and operation year) standard population was a secondary outcome. Additionally, 90-days mortality rate, variables associated with mortality and causes of late death (based on CDR) were also evaluated.

Statistics

Kaplan-Meier analysis with log-rank test was used to assess long-time survival (before and after stratifications) and on the subgroup of patients alive at 90 days with comparison against a matched standard population. Mortality within 90 days and patient characteristics were assessed with chi-square for categorized variables and ANOVA for continuous variables, (with Bonferroni corrected P values). To evaluate the effect of different risk variables, cox-regression analysis was used for overall mortality and multivariable logistic regression for 90-day mortality. The selection of variables was done by univariate screen of all available confounders from the data extraction, using backwards selection with a criteria of 0.25 to stay in the regression models. Two sided tests were used, and p values <0.05 were considered statistically significant. Data management and statistical analysis were performed with SPSS statistics version 24 (IBM, Armonk, NY, USA).

Study IV

In this study, the aim was to assess the epidemiology and the surgical outcome after dTAA repair in Sweden. All individuals who had an operation due to a dTAA (intact or ruptured) 1997 to 2017 (21 years) in Sweden were identified from NPR and CDR and merged into one database. Because all thoracic aneurysms have the same diagnostic ICD code (only separated by intact or rupture), the anatomical location of the aneurysm had to be controlled by the NCSP operation code. To isolate dTAA subjects, patients with codes for ascending aortic surgery and patients with an additionally code for dissection were excluded, Figure 3.

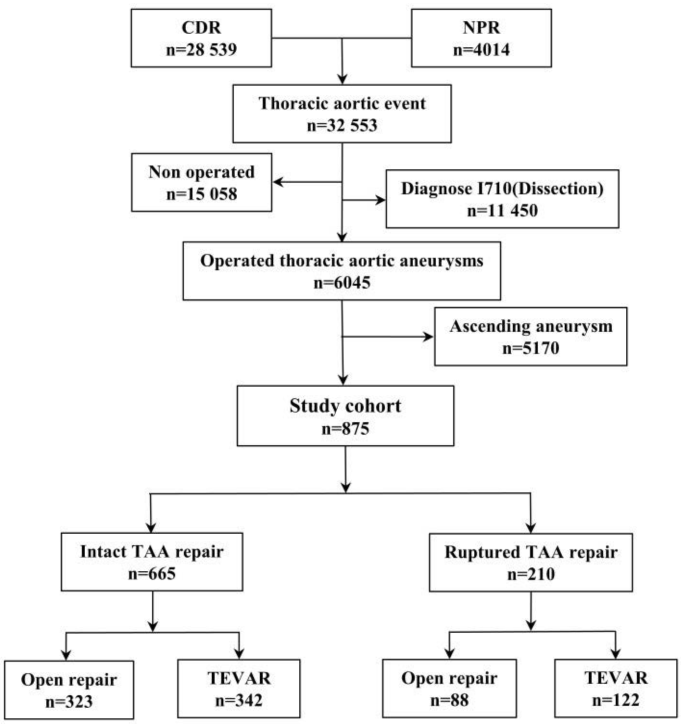

Figure 3. Flowchart of the study cohort from CDR (cause of death register) and NPR (national patient register)

The cohort was stratified into intact or ruptured dTAA and gender. For mortality and survival analysis the cohort were divided into three 7-year groups (1997-2003, 2004-2010 and 2011-2017).The primary outcomes of the study was to identify the incidence of surgically treated dTAA in Sweden and the subsequent short- (<90-days) and, medium-term (1-year) mortality and long-term (5-year) survival outcome. Secondary endpoint were to assess changes in incidence of repair and outcome over time with increasing use of TEVAR.

Statistics

Patients' characteristics were evaluated with Chi-square and ANOVA for categorized and continuous variables with Bonferroni corrected P-values. Trends of incidence in intact and ruptured dTAA repair (presented per 100.000 person-year) were evaluated with linear regression. Crude mortality rates were assessed with chi-square and survival with Kaplan-Meier curve adjusted for comorbidity, age and operation technique. Cox proportional hazard model was constructed to assess independent variables on the risk for short- and long-term mortality. A two-tailed p-value of <0.05 was considered significant. All statistical analyses were performed using SPSS v. 25.0. Armonk, NY: IBM Corp.

Ethical considerations

All four studies were approved by the regional ethics review board in Uppsala (Dnr: 2014/078), for study III and IV, a supplement was made (Dnr: 2019-05615) to the primary ethical approval to get an extension of time and previous contacts with the healthcare system to capture comorbidities.

All data was collected from registries and an assessment was made from the board that no consent from the included patients was needed.

Data from register extracts have been stored and processed on Region Gävleborg encrypted servers which are assigned to handle patient and research data according to General Data Protection Regulation (GDPR). Data extractions were protected with code keys provided from the National Board of Health and Welfare in Sweden.

Results

Study I

There were 1304 operations performed (EVAR on 26.3%, n=343) at 29 operating centres. Twelve centres did not use EVAR as an operation method for aortic ruptures during the study period. Three centres used EVAR on >50% of their RAAAs and were regarded as pEVARc, leaving 26 centres as pORc, Figure 4. All pEVARc and five of the pORc were regarded to be referral centres.

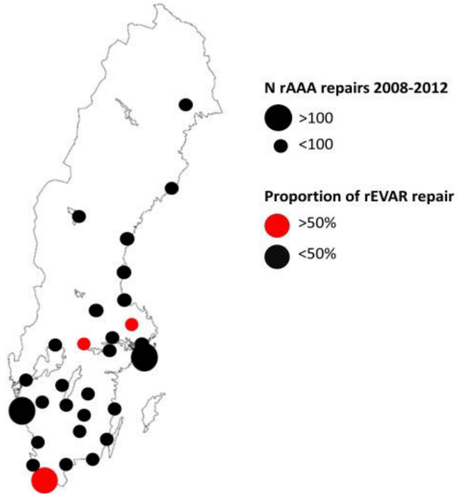

Figure 4. Distribution of centres performing ruptured abdominal aortic aneurysm (rAAA) repair in Sweden, based on size and proportion of ruptured endovascular repair (rEVAR). Reproduced from Gunnarsson K et al. *Endovascular Versus Open Repair as Primary Strategy for Ruptured Abdominal Aortic Aneurysm: A National Population-based Study.* Eur J Vasc Endovasc Surg 2016.

Primary EVAR centres treated 236 patients (74.6% of whom were operated with EVAR) and pORc treated 1068 patients (15.6% of whom were operated with EVAR), Figure 5.

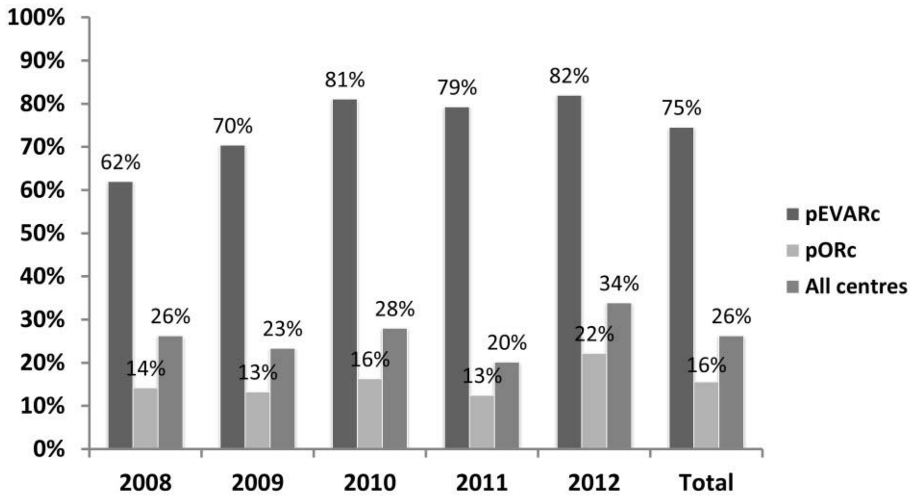

Figure 5. Proportion of EVAR at primary EVAR centres (pEVARc) and primary open repair centres (pORc) as well as overall use of EVAR for treatment of ruptures in Sweden during different years.

Patients treated at pEVARc were more often referrals, had a higher rate of pulmonary comorbidity, higher systolic blood pressure before surgery and EVAR operated patients at pEVARc had a higher rate of pre-operative loss of consciousness compared to EVAR treated at pORc. Regarding perioperative complications, there was a lower proportion of patients with a massive peri-operative blood loss at pEVARc but at the same time, the proportion of laparotomy due to ACS was twice as high compared to pORc (10% vs 5%; p=0.03) and endoleaks was a more common problem. Table 4.

Table 4. *Peri-operative complications*

Perioperative complications.	**pEVARc**	**pORc**	**p-value**
Total number of patients	236	1068	
>5litres of bleeding, n (%)	**35 (14.9)**	**315 (29.5)**	**<0.001**
Myocardial infarction, n (%)	11 (6.3)	53 (5.9)	0.862
Stroke, n (%)	5 (2.8)	18 (2.1)	0.566
Renal failure, n (%)	42 (23.5)	203 (22.3)	0.769
Multiple organ failure, n (%)	29 (17.1)	167 (18.5)	0.746
Reoperation for bleeding, n (%)	17 (9.5)	68 (7.4)	0.357
ACS with laparotomy, n (%)	**17 (9.5)**	**47 (5.1)**	**0.034**
Intestinal ischaemia, n (%)	14 (7.8)	96 (10.7)	0.281
Limb amputation, n (%)	4 (2.2)	16 (1.7)	0.551
Graft occlusion, n (%)	1 (0.7)	10 (1.2)	1.000
Endoleakage, n (%)	**13 (7.4)**	**12 (1.3)**	**<0.001**
Distal embolization, n (%)	9 (5.0)	65 (7.1)	0.415
Early graft infection, n (%)	4 (2.2)	6 (0.7)	0.065
ICU >5 days, n (%)	44 (27.2)	263 (32.1)	0.229

n= numbers, ACS= abdominal compartment syndrome, ICU= intensive care unit

When assessing mortality between the two centre strategies no difference could be detected in peri-operative, mid- or long-term mortality overall. Figure 6 and 7A. Notably, pEVARc had higher 1- and 2-year OSR mortality.

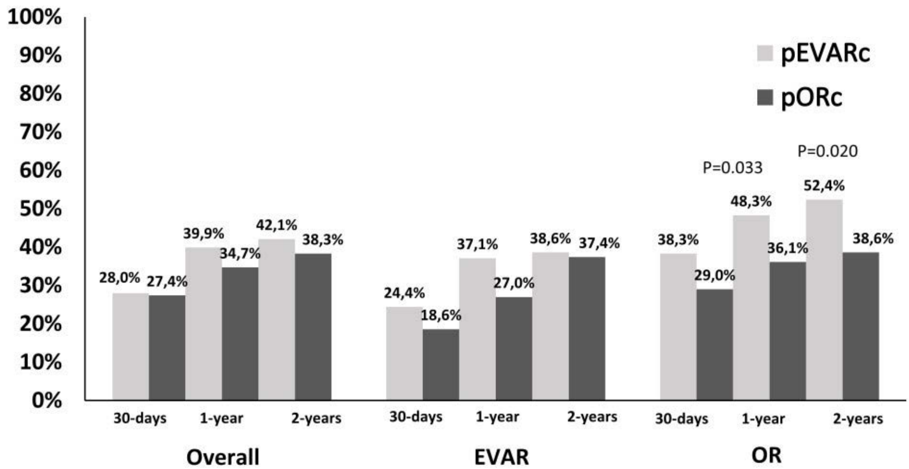

Figure 6. Post-operative mortality after ruptured abdominal aortic aneurysm repair at primary EVAR centres (pEVARc) and primary open repair centres (pORc).

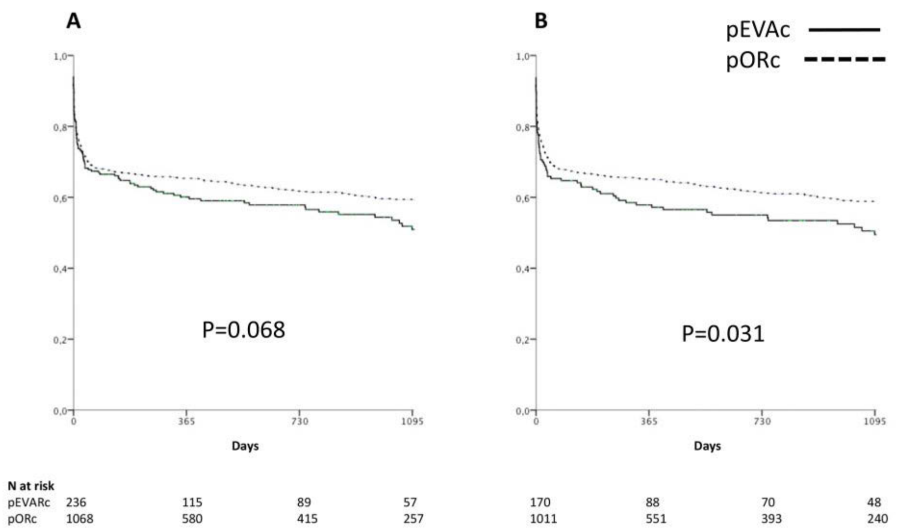

Figure 7. Kaplan-Meier analysis of long-term overall survival after ruptured abdominal aortic aneurysm repair 2008-2012 in Sweden at centres with primary EVAR strategy (pEVARc) and primary open repair strategy (pORc). **A)** All patients; **B)** excluding referrals

Subgroups analyses of peri-operative, 1- and 2-year mortality were performed on octogenarians without no difference in mortality.

Comparing operation method and not strategy, patients treated with EVAR were generally older (76.4 vs. 74.0 years; $p<0.01$), had a higher pre-operative systolic blood pressure, and were more often referrals compared to OSR. Mortality rate was lower in patients operated with EVAR at 30-days (EVAR 21.6%, n =74; open repair 29.6%, n=288, $p<0.01$) but no significant difference was seen at 1- or 2-year. Comparing method between pEVARc vs pORc, mortality was lower for EVAR regardless of where these patients were operated. Twelve centres did not perform any EVAR for ruptures. The open repair mortality in these centres was 24.3% compared with 32.1% after open repair in centres performing any ruptured EVAR (p=0.02). However, owing to the lower EVAR mortality, the overall mortality for rupture did not differ between these groups. Patients with a pre-operative loss of consciousness had a higher mortality rate both after open repair and EVAR (OR 34.6% vs. 25.3%; EVAR 31.2% vs. 16.0%, $p<0.01$). To analyse predictive factors for perioperative mortality after RAAA a univariate analysis was conducted. Female sex, age, cardiac- pulmonary- disease, decreased renal function together with mentioned pre-operative loss of consciousness were pointed out. In the multivariate analysis age, pre-operative loss of consciousness and decreased renal function remained significant.

To evaluate the impact of referred patients to pEVARc, data were scrutinized to assess mortality outcome. Referrals were younger (73.3 years vs. 74.8 years; p=0.05), and had a higher pre-operative systolic blood pressure. No difference between referred and non-referred patients in mortality was detected. To evaluate the mortality outcome at the pEVARc and pORc, an exclusion of the referral cases from mortality analysis was made. This did not affect mortality up to 2 years, but displayed a higher mortality in pEVARc over time. Figure 7B. Allocating back referred patients to their primary uptake disclosed that the incidence RAAA repair per 100,000 inhabitants was lower in pEVARc regions compared to pORc regions (6.07 per 100,000 inhabitants, 95% confidence interval (CI) 5.01-7.13 vs 8.15 per 100,000 inhabitants, 95% CI 7.64-8.66).

Study II

18,726 registered patients with RAAA were identified in the three registries. The contribution of each registry to this cohort is described in a Venn diagram, Figure 8. 74 % of all ruptures were among men (unchanged ratio over time) and both men and women affected by RAAA had a progressively increasing age over time (p<0.001).

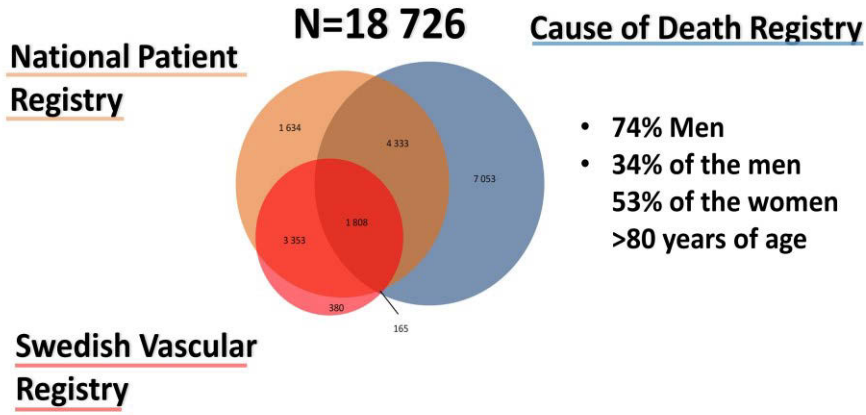

Figure 8. Overlap between the three registries. All RAAA patients in Sweden 1994-2013, collected from Swedvasc, CDR and NPR.

The proportion who underwent RAAA surgery with EVAR increased both in men 0.2%: 1994-1998 to 15.5%: 2009-2013 (p<0.001) and women 0.1%: 1994-1998 to 9.6%: 2009-2013 (p<0.001) over time. Notably, the mean age of those who were operated on, increased in men but not among women. There was an overall decrease in the incidence of RAAA with 35% during the study period (p=0.001). Among men the incidence decreased with 45% and among men <80 years of age, a decrease of 60% (-1.41 per 100,000 annually, p=0.001) occurred. In women there was almost no change in the incidence over time, Figure 9A. Overall, the total number of RAAA presenting to hospital annually decreased from 1994 to 2013 with 94 patients (-15.2%). The annual incidence per 100,000 person-years presenting to hospital decreased in men overall, Figure 9B, and among men <80 years of age (-0.91 per 100,000 person years annually, p<0.001) but no change among octogenarians over time was detected.

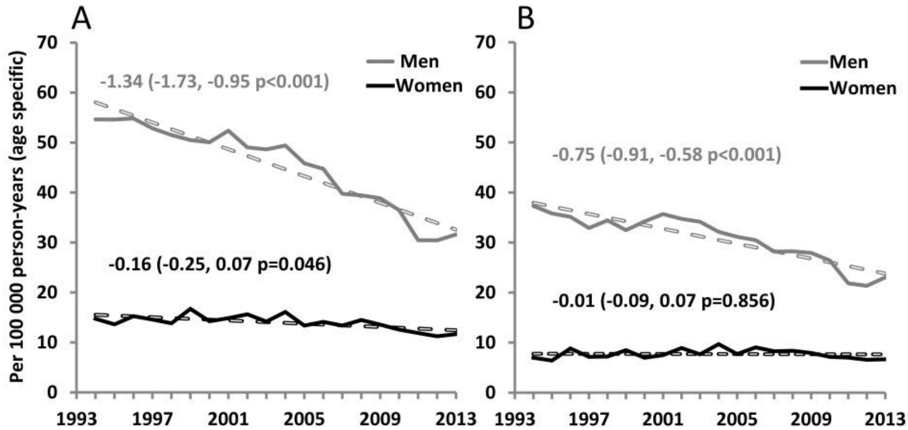

Figure 9. **A)** Yearly incidences of ruptured AAA and **B)** Ruptured AAA presenting to hospital per 100,000 person-years, overall for Men and Women. Linear regression trend lines are presented, with yearly coefficient, 95% confidence interval (CI) and P-value.

A small decrease among women <80 years of age (-0.06 per 100,000 person years annually, p=0.024) was detected but the incidence was stable for octogenarians and overall (Figure 9B). The proportion of patients with RAAA that presented to hospitals alive increased over time both among men and women, Table 5. Of all RAAA patients in the study cohort, 65% arrived to hospital and therefore had a possibility to be operated, time trends is assessed in Table 5. Between 1994-1998 and 2009-2013, the proportion of, patients with RAAA who were admitted to hospital alive increased among men and women with 10.0% and 13.2 % in relative change (RC) respectively. The most noticeable increase was among male octogenarians (Table 5).

Of all the patients in this study cohort 48.6% of the men and 28.1% of the women had some type of aortic surgery due to rupture. Assessing the proportion of patients with RAAA repaired, men and women both had a significant increase where octogenarians had an increase of almost 50% (men 44.3% and women 49.3%, p<0.001) from the first to the last time period. The turn-down rate (patients arriving to hospital alive but were not operated on) decreased during the study period among men (RC -16.0%, p<0.001) and women (RC -14.0%, p=0.002) (Table 5) and was 33.4% during the entire study period.

In the first year of this study 1994, EVAR was still not established as a surgical option for RAAA treatment. The first EVAR for RAAA was detected 1995 in this cohort. During the following 20 years, an increasing proportion of RAAA repairs were performed with EVAR; and in 2013, 42.3% of the men

Table 5. *Proportion RAAA patients presenting to a hospital alive, proportion repaired, 90-days mortality among all RAAA patients and among patients undergoing RAAA repair.*

		RAAA presenting to hospital			Proportion repaired RAAA			All RAAA Mortality			Repaired RAAA Mortality		
	5-year groups	to hospital	RC (95% CI)	p-value	Repaired	RC (95% CI)	p-value	Mortality	RC (95% CI)	p-value	Mortality	RC (95% CI)	p-value
Men													
Total	1994-1998	65.4%	Reference		44.5%	Reference		75.8%	Reference		47.0%	Reference	
	1999-2003	68.4%	+4.6% (1.3,8.0)	0.005	47.6%	+6.9% (2.1,12.0)	0.004	69.7%	-8.1% (-10.5,-5.6)	<0.001	38.2%	-18.6% (-24.3,-12.5)	<0.001
	2004-2008	68.6%	+4.9% (1.6,8.4)	0.004	47.9%	+7.6% (2.7,12.8)	0.002	67.9%	-10.4% (-12.8,-7.9)	<0.001	36.0%	-23.3% (-28.8,-17.2)	<0.001
	2009-2013	71.9%	+10.0 (6.5,13.7)	<0.001	49.7%	+11.7% (6.3,17.4)	<0.001	64.8%	-14.5% (-17.1,-11.8)	<0.001	31.8%	-32.3% (-37.9,-26.2)	<0.001
50-79 years	1994-1998	66.6%	Reference		54.3%	Reference		69.0%	Reference		42.4%	Reference	
	1999-2003	69.8%	+4.8% (1.0,8.7)	0.014	57.0%	+4.8% (-0.1,10.1)	0.056	62.8%	-9.1% (-12.5,-5.5)	<0.001	34.2%	-19.3% (-26.2,-11.2)	<0.001
	2004-2008	69.3%	+4.0% (0.0,8.1)	0.049	59.8%	+10.0% (4.7,15.5)	<0.001	58.4%	-15.4% (-19.0,-11.6)	<0.001	30.0%	-29.2% (-35.9,-21.8)	<0.001
	2009-2013	69.8%	+4.8% (1.0,8.7)	0.027	59.7%	+9.8% (4.2,15.8)	<0.001	57.3%	-17.0% (-21.0,-12.8)	<0.001	28.3%	-33.3% (-40.5,-25.2)	<0.001
≥80 years	1994-1998	62.0%	Reference		24.3%	Reference		90.6%	Reference		65.2%	Reference	
	1999-2003	65.2%	+5.1% (-1.1,11.7)	0.109	29.0%	+19.5% (6.4,34.2)	0.003	85.0%	-6.2% (-9.0,-3.3)	<0.001	55.0%	-15.6% (-36.4,-5.0)	0.005
	2004-2008	67.6%	+8.9% (2.7,15.5)	0.004	28.9%	+19.2% (6.1,33.9)	0.003	86.6%	-4.4% (-7.1,-1.7)	0.002	58.9%	-9.6% (-19.3,1.2)	0.081
	2009-2013	75.2%	+21.3% (14.5,28.4)	<0.001	35.0%	+44.3% (28.6,61.9)	<0.001	79.9%	-11.8% (-14.7,-8.7)	<0.001	47.3%	-27.5% (-40.4,-17.3)	<0.001
Women													
Total	1994-1998	51.1%	Reference		22.3%	Reference		88.5%	Reference		51.8%	Reference	
	1999-2003	52.3%	+2.4% (-5.2,10.5)	0.551	23.8%	+6.8% (-6.7,22.2)	0.342	87.6%	-1.1% (-3.9,1.9)	0.474	51.4%	-0.8% (-14.8,15.5)	0.922
	2004-2008	60.2%	+17.9% (9.8,26.7)	<0.001	31.2%	+40.1% (23.7,58.6)	<0.001	81.4%	-8.1% (-11.0,-5.1)	<0.001	45.0%	-13.2% (-25.4,10.0)	0.067
	2009-2013	57.9%	+13.2 (5.1,22.0)	0.001	28.2%	+26.4% (10.6,44.4)	<0.001	82.2%	-7.1% (-10.2,-3.9)	<0.001	41.4%	-20.1% (-32.6,-5.3)	0.010
50-79 years	1994-1998	48.8%	Reference		33.2%	Reference		84.2%	Reference		51.7%	Reference	
	1999-2003	52.5%	+7.6% (-3.6,20.0)	0.190	35.3%	+6.5% (-8.7,24.3)	0.423	82.8%	-1.7% (-6.4,3.3)	0.504	50.5%	-2.2% (-18.5,17.3)	0.807
	2004-2008	62.0%	+27.0% (14.6,40.7)	<0.001	48.6%	+46.5% (27.4,68.5)	<0.001	70.5%	-16.3% (-21.4,-10.9)	<0.001	39.3%	-24.1% (-37.4,-7.9)	0.005
	2009-2013	53.6%	+9.7% (-2.2,23.0)	0.114	40.3%	+21.5% (3.9,41.9)	0.014	73.8%	-12.3% (-17.8,-6.5)	<0.001	35.2%	-31.9% (-46.1,-14.0)	0.001
≥80 years	1994-1998	53.2%	Reference		12.5%	Reference		92.5%	Reference		50.3%	Reference	
	1999-2003	51.9%	-2.3% (-12.2,8.6)	0.666	13.6%	+8.9% (-15.3,40.2)	0.506	92.5%	-0.1% (-3.2,3.2)	0.969	53.7%	6.7% (-18.7,40.2)	0.639
	2004-2008	59.0%	+10.9% (0.4,22.6)	0.041	17.4%	+39.0% (9.4,76.7)	0.007	91.1%	-1.5% (-4.7,1.7)	0.359	56.6%	12.5% (-13.0,45.5)	0.369
	2009-2013	61.4%	+15.4% (4.5,27.5)	0.005	18.6%	+49.3% (17.3,90.1)	0.001	89.8%	-3.1% (-6.3,0.5)	0.092	52.4%	4.1% (-20.5,36.4)	0.769

CI= confidence interval, RC= relative chance, RAAA= ruptured abdominal aortic aneurysm and 41.2% of the women had surgery with EVAR for RAAA. EVAR has had even a greater impact on elderly patients as rupture treatment. Among octogenarians, EVAR was used in 59.3% of men with RAAA, and in 50.0% of women. Patients affected by a RAAA had a 90-day mortality of 74.7% overall, 71.0% in men, and 85.3% in women, p<0.001. The 90-day mortality per 100,000 age-specific person-years decreased both among men and woman in total (men 40.5 and women 12.8 per 100,000 in 1994 vs 21.4 and 9.9 per 100,000 in 2013, p<0.001). This decrease was also detected among the younger patients in both sexes, but was stable among female octogenarians, Figure 10A and B.

Assessing the time trends in 90-days mortality, there was a decrease in mortality among men overall as well as in women <80 years. Time trends in mortality per 5-year period are presented in Table 5. Among repaired patients similar trends were seen (Table 5). When adjusting surgical mortality for the increased use of EVAR, a reduction in the improved 90-day mortality after repair was seen, indicating that the improved outcome of surgery over time is due to EVAR.

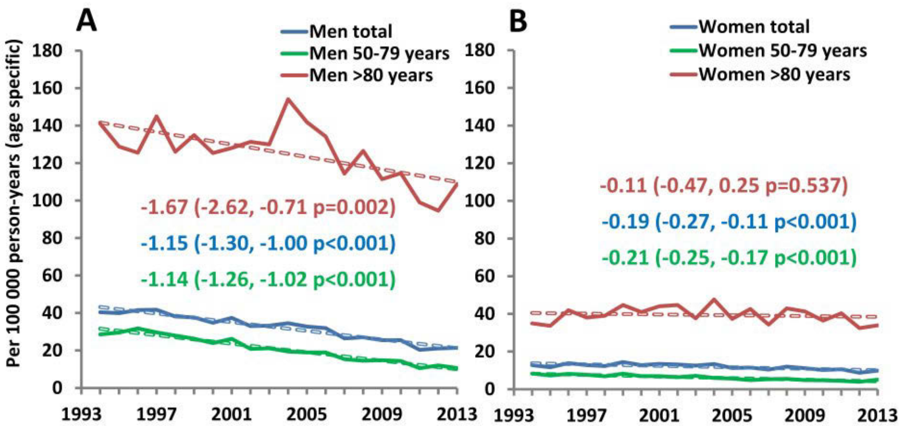

Figure 10. Mortality in ruptured AAA per 100,000 person-years, overall and per age-group for **A)** Men and **B)** Women. Linear regression trend lines are presented with yearly coefficient, 95% CI and P-value.

Study III

8,928 registered individuals with RAAA were identified in the three registries and distributed into three time periods: 1994-2001: N=3,368; 2002-2009: N=3,405; 2010-2017: N=2,155. During the time of the study, an increase in the proportion of EVAR procedures was noted and was higher among octogenarians compared to younger patients operated for RAAA, Figure 11.

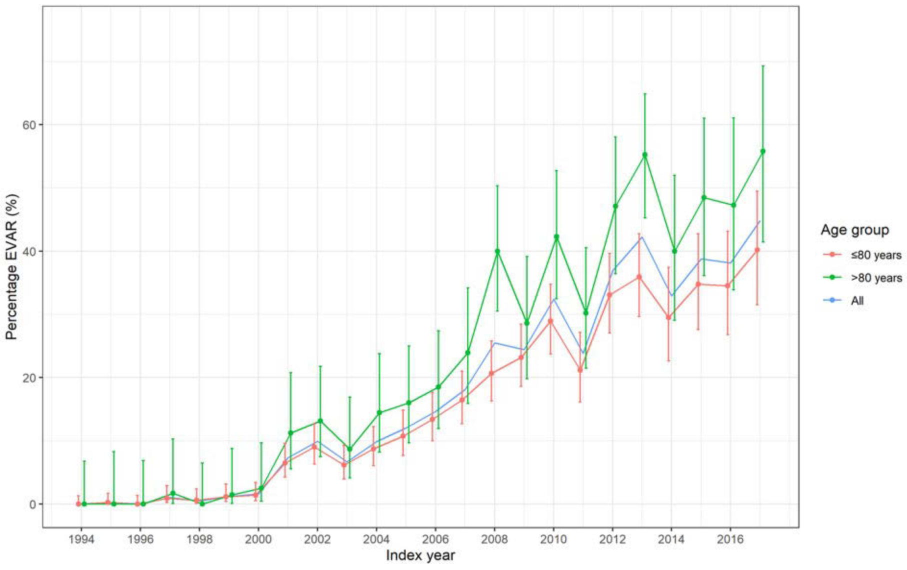

Figure 11. Time trend of proportion of EVAR used for ruptured AAA repairs after age stratification.

Of the individuals that received RAAA repair, the following trends were identified: increase in mean age (+ 2.3 years, p<0.001), proportion octogenarians, (+ 13.4%, p<0.001), proportion of operated women (+6.2%, p<0.001), proportion of EVAR procedures (+34.0%, p<0.001) as well as medical comorbidities during the timeframe of analysis, Table 6.

The short term mortality (<90-days) was 40.7% for the entire cohort and decreased over time (from 46.4%; 1994-2001 to 35.6%; 2010-2017; p<0.001) partly due to that EVAR in multivariable logistic regression were independently associated with lower odds of 90-day mortality. The overall crude long-term survival (5-year survival) were assessed with a Kaplan-Meier analysis, stratified by period of repair and age-separation (<80 or >80 years of age). This displayed improved long-term survival over time in the total cohort (36%; 1994-2001: 44%; 2002-2009 43%; 2010-2017; p<0.001).

Table 6. *Patient characteristics*

	Overall	1994-2001	2002-2009	2010-2017	p
Number of patients	(N=8928)	(N=3368)	(N=3405)	(N=2155)	
Mean age, Y (SD)	74.04 (7.78)	73.21 (7.44)	73.94 (7.92)	75.49 (7.89)	<0.001
Octogenarians	2364(26.5%)	694(20.6%)	937(27.5%)	733(34.0%)	<0.001
Females	1555(14.4%)	481(14.3%)	631(18.5%)	443(20.6%)	<0.001
Proportion EVAR	1323(14.8%)	52(1.5%)	506(14.9%)	765(35.5%)	<0.001
Cardiac disease	4237(48.0%)	1480(44.0%)	1751(51.4%)	1006(48.9%)	<0.001
Pulmonary disease	1575(17.9%)	463(13.8%)	6445(18.9%)	467(22.8%)	<0.001
Cerebrovascular disease	1600(18.2%)	569(16.9%)	634(18.6%)	397(19.4%)	0.044
Diabetes	904(10.2%)	228(6.8%)	371(10.9%)	305(14.7%)	<0.001
Renal disease	1278(14.8%)	370(11.0%)	517(15.2%)	391(20.7%)	<0.001
Cancer	1245(15.2%)	142(4.2%)	626(18.4%)	477(32.8%)	<0.001
Dementia	115(1.4%)	30(0.9%)	58(1.7%)	27(1.9%)	0.005
Artery disease	238(2.9%)	74(2.2%)	103(3.0%)	61(4.2%)	0.001
Liver disease	58(0.7%)	13(0.4%)	30(0.9%)	15(1.0%)	0.014

SD= standard deviation, Y= years, EVAR= endovascular aortic repair

In the age-separated analysis, long-term survival were improved in both age groups over time (at 5 years:<80 years of age 40% vs 51% vs 52%, p<0.001; octogenarians19% vs 24% vs 25%, p=0.001), Figure 12.

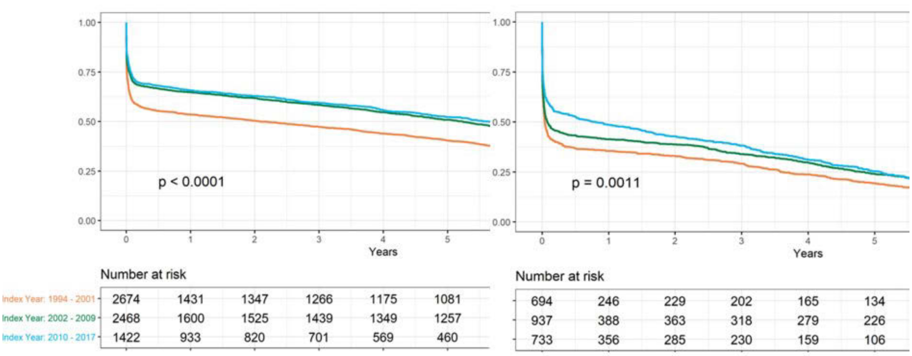

Figure 12. Kaplan-Meier analysis of long-term survival on patients <80 years (left) and octogenarians (right) stratified into the three time periods

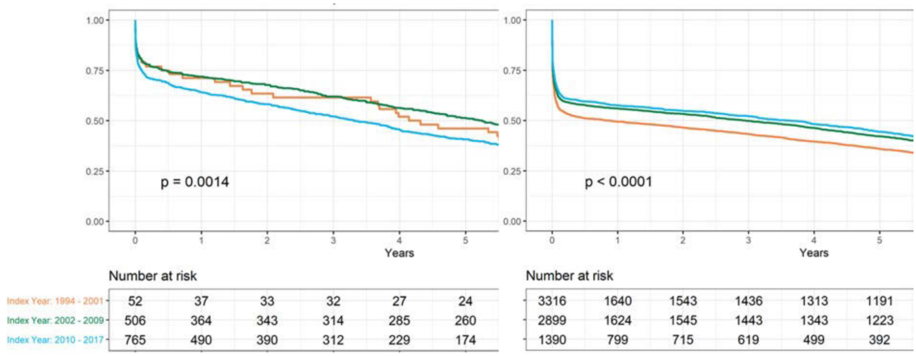

Figure 13. Kaplan-Meier analysis of long-term survival on endovascular (left) and open (right) aortic repair, stratified into the three time periods.

When assessing long-term survival after stratifying into operation technique, EVAR had a decrease (at 5-years 46%, 51%, 41%, p=0.001) whilst OSR improved (36%, 42%, 44%, p<0.001), Figure 13. An analysis comparing the long-term survival, EVAR vs OSR in an unadjusted Kaplan-Meier analysis, endovascular repair had a lower mortality early but similar survival at 5-years. To assess the effect of independent variables associated with long time mortality, cox-proportional hazard analysis was done. Increasing age (HR=1.05, P=0.001), female gender (HR=1.12, P<0.001) was associated, with increased overall mortality. Use of EVAR (HR=0.80, P<0.001) was associated with lower mortality as was the period of repair, Table 7.

Table 7. *Cox proportional model for overall mortality*

	HR	95% CI	P value
1994-2001		Reference	
2001-2008	0.80	0.75-0.84	<0.001
2008-2017	0.72	0.67-0.78	<0.001
Age	1.05	1.05-1.06	<0.001
Women	1.12	1.05-1.19	<0.001
EVAR	0.80	0.74-0.86	<0.001
Cardiac disease	1.12	1.07-1.18	<0.001
Pulmonary disease	1.22	1.15-1.30	<0.001
Cerebrovascular disease	1.24	1.17-1.32	<0.001
Diabetes	1.11	1.02-1.20	0.012
Renal disease	1.20	1.13-1.29	<0.001
Cancer	1.18	1.10-1.27	<0.001
Dementia	1.36	1.12-1.64	0.002
Peripheral artery disease	1.298	1.13-1.49	<0.001
Liver disease	1.40	1.06-1.85	0.017

HR= hazard ratio, CI= confidence interval, EVAR= endovascular aortic repair

To assess the relative survival of RAAA repaired patients that had survived >90-days, an analysis against a matched (age, sex and year of operation) population cohort as referents was done. Repaired patients had lower relative 5-year survival than the matched population referents in all three time-periods (1994-2001: 86%, 2002-2009: 88%, 2010-2017: 86%; p<0.001), Figure 14.

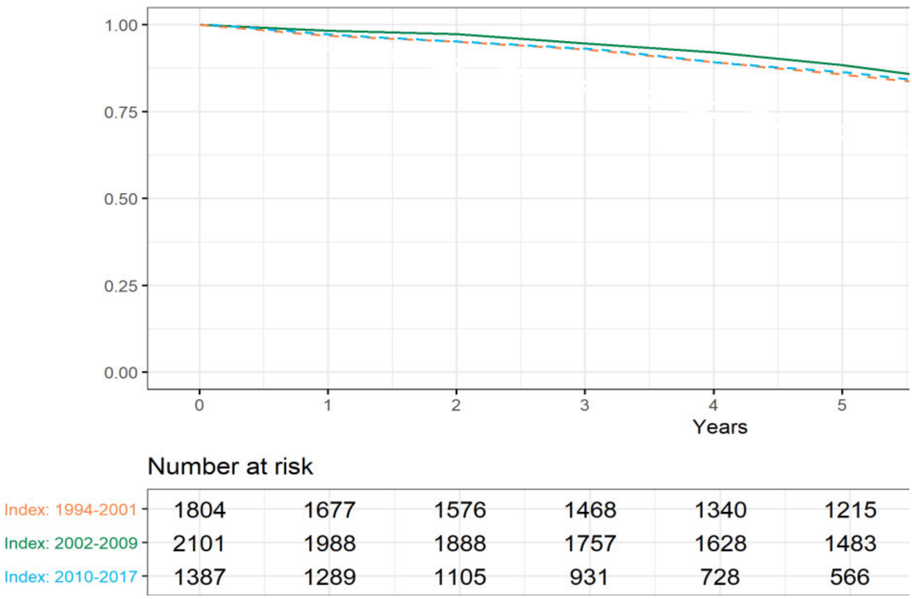

Figure 14. Kaplan-Meier analysis of relative survival for patients surviving >90 days after repair compared with a matched (age, sex and year of operation) standard population.

Comparing the study cohort with the matched cohort to assess survival ratio revealed that relative survival did not improve during the time of the study. The median survival time was for period one, 7.8 RAA cohort vs 12.2 Years for matched cohort (median survival ratio, 0.63: 95% CI 0.61-0.67), period two, 8.4 vs 12.8 years (median survival ratio, 0.65: 95% CI 0.62-0.68), period three, 7.7 vs 12.1 years (median survival ratio, 0.63: 95% CI 0.59-0.69.)

Operated RAAA patients that survived >90 days and died during the study period was analysed to identify causes of late death, Figure 15. A decrease was noted for cardiovascular and cancer related deaths over time (Figure 15) and together they accounted for 55% of all late deaths.

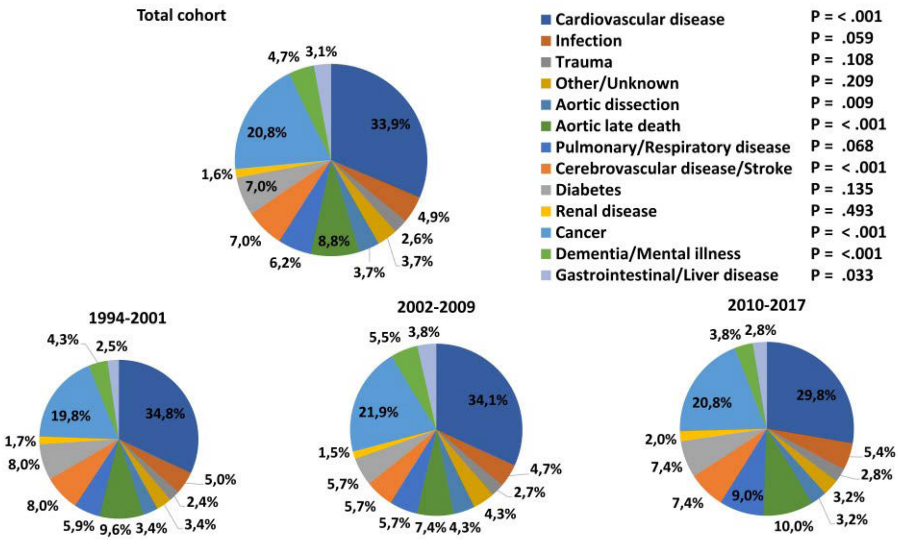

Figure 15. Causes of late deaths.

Study IV

From NPR and CDR there were 875 individuals identified who between 1997 and 2017 underwent surgery for a dTAA, 63.8% (558) were men, 24.0% (210) had ruptured dTAA repair. Both men and women operated for dTAA had over time progressively increasing mean age and rate of comorbidities and 10.2% (89) of the patients were octogenarians, Table 8. Over time, an increasing proportion of patients undergoing ruptured dTAA repair were women, with almost half of the repairs performed on women in the study found in the final time period (Table 8). The incidence of ruptured dTAA repair overall, was stable during the study period, Figure 16.

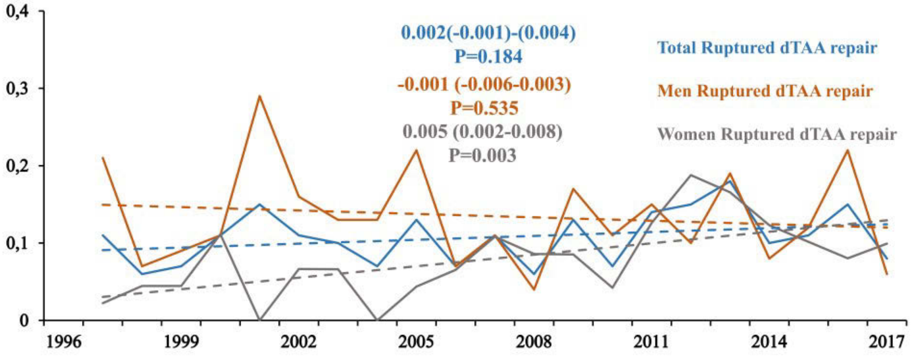

Figure 16. Incidence of ruptured descending thoracic aortic aneurysm repair per 100,000 population, in total, men and women (coefficient, 95% CI and P-value).

Table 8. *Patient characteristics among individuals undergoing rupture or intact thoracic aortic aneurysm repair in Sweden during 21 years (1997-2017).*

	Ruptured dTAA repair					Intact dTAA repair				
	Total	1997-2003	2004-2010	2011-2017	p-value	Total	1997-2003	2004-2010	2011-2017	p-value
Total, (n)	210	63	59	88		665	140	257	268	
Men, % (n)	62.4% (131)	74.6% (47)	66.1% (39)	51.1% (45)	0.011	64.2% (427)	64.3% (90)	63.0% (162)	65.3% (175)	0.864
Mean age, years (SD)	71.0 (11.4)	69.2 (12.2)	71.3 (10.6)	72.1 (11.3)	0.288	68.6 (10.5)	64.0 (11.5)	68.3 (11.0)	71.3 (8.5)	<0.001
Octogenarians, % (n)	19.5% (41)	17.5% (11)	13.6% (8)	25.0% (22)	0.206	7.2% (48)	2.1% (3)	5.4% (14)	11.6% (31)	0.001
TEVAR, % (n)	58.1% (122)	12.7% (8)	64.4% (38)	86.4% (76)	<0.001	51.4% (342)	7.1% (10)	49.8% (128)	76.1% (204)	<0.001
Cardiac disease	38.1% (80)	23.8% (15)	40.7% (24)	46.6% (41)	0.005	56.1% (373)	47.1% (66)	63.8% (164)	53.4% (143)	0.593
Pulmonary disease	22.4% (47)	9.5% (6)	27.1% (16)	28.4% (25)	0.008	20.5% (136)	9.3% (13)	21.4% (55)	25.4% (68)	<0.001
Cerebrovascular disease	10.0% (21)	7.9% (5)	11.9% (7)	10.2% (9)	0.682	9.8% (65)	2.1% (3)	10.5% (27)	13.1% (35)	0.001
Diabetes	11.0% (23)	7.9% (5)	6.8% (4)	15.9% (14)	0.100	11.7% (78)	2.9% (4)	13.2% (34)	14.9% (40)	0.001
Renal disease	11.9% (25)	6.3% (4)	8.5% (5)	18.2% (16)	0.022	12.2% (81)	7.9% (11)	11.7% (30)	14.9% (40)	0.036
Men										
Mean age, years (SD)	70.4 (12.5)	69.2 (11.5)	70.6 (12.4)	71.6 (13.8)	0.649	67.9 (11.0)	63.1 (12.3)	66.9 (11.1)	71.3 (9.0)	<0.001
Octogenarians, % (n)	19.1% (25)	10.6% (5)	15.4% (6)	31.1% (14)	0.013	7.5% (32)	1.1% (1)	4.9% (8)	13.1% (23)	<0.001
TEVAR, % (n)	51.9% (68)	12.8% (6)	64.1% (25)	82.2% (37)	<0.001	49.4% (211)	7.8% (7)	46.9% (76)	73.1% (128)	<0.001
Cardiac disease	38.2% (50)	23.4% (11)	48.7% (19)	44.4% (20)	0.037	58.3% (249)	47.8% (43)	66.0% (107)	56.6% (99)	0.408
Pulmonary disease	15.3% (20)	6.4% (3)	17.9% (7)	22.2% (10)	0.035	19.4% (83)	10.0% (9)	21.6% (35)	22.3% (39)	0.031
Cerebrovascular disease	10.7% (14)	10.6% (5)	7.7% (3)	13.3% (6)	0.683	9.8% (42)	2.2% (2)	11.1% (18)	12.6% (22)	0.013
Diabetes	6.9% (9)	6.4% (3)	5.1% (2)	8.9% (4)	0.640	11.7% (50)	2.2% (2)	12.3% (20)	16.0% (28)	0.002
Renal disease	11.5% (15)	6.4% (3)	7.7% (3)	20.0% (9)	0.042	14.1% (60)	5.6% (5)	14.8% (24)	17.7% (31)	0.010
Women										
Total (n)	79	16	20	43		238	50	95	93	
Mean age, years (SD)	71.9 (9.2)	69.2 (14.6)	72.5 (66.0)	72.7 (7.9)	0.419	69.8 (9.5)	65.6 (9.7)	70.5 (10.5)	71.3 (7.6)	0.002
Octogenarians, % (n)	20.3% (16)	37.5% (6)	10.0% (2)	18.6% (8)	0.287	6.7% (16)	4.0% (2)	6.3% (6)	8.6% (8)	0.287
TEVAR, % (n)	68.4% (54)	12.5% (2)	65.0% (13)	90.7% (39)	<0.001	55.0% (131)	6.0% (3)	54.7% (52)	81.7% (76)	<0.001
Cardiac disease	38% (30)	25.0% (4)	25.0% (5)	48.8% (21)	0.050	52.1% (124)	46.0% (23)	60.0% (57)	47.3% (44)	0.810
Pulmonary disease	34.2% (27)	18.8% (3)	45.0% (9)	34.9% (15)	0.410	22.3% (53)	8.0% (4)	21.1% (20)	31.2% (29)	0.001
Cerebrovascular disease	8.9% (7)	0.0% (0)	20.0% (4)	7.0% (3)	0.763	9.7% (23)	2.0% (1)	9.5% (9)	14.0% (13)	0.023
Diabetes	17.7% (14)	12.5% (2)	10.0% (2)	23.3% (10)	0.236	11.8% (28)	4.0% (2)	14.7% (14)	12.9% (12)	0.188
Renal disease	12.7% (10)	6.3% (1)	10.0% (2)	16.3% (7)	0.274	8.8% (21)	12.0% (6)	6.3% (6)	9.7% (9)	0.810

N= number, SD= standard deviation, dTAA= descending thoracic aortic aneurysm, TEVAR= thoracic endovascular aortic aneurysm repair

Table 9. *Incidence of thoracic aortic aneurysm repair per 100.000 population*

		1997-2003	2004-2010	2011-2017	annual co-efficients	p-value
Intact dTAA repair						
<80 years of age	**Total**	0.23	0.40	0.37	0.011	0.007
	Men	0.30	0.50	0.46	0.012	0.020
	Women	0.16	0.29	0.27	0.010	0.008
≥80 years of age	**Total**	0.09	0.40	0.88	0.060	<0.001
	Men	0.09	0.63	1.70	0.122	<0.001
	Women	0.09	0.27	0.37	0.022	0.041
Ruptured dTAA repair						
<80 years of age	**Total**	0.09	0.08	0.10	0.001	0.589
	Men	0.14	0.11	0.09	-0.004	0.069
	Women	0.03	0.06	0.11	0.005	0.001
≥80 years of age	**Total**	0.34	0.23	0.63	0.023	0.075
	Men	0.43	0.48	1.04	0.050	0.077
	Women	0.29	0.09	0.37	0.005	0.593

dTAA= descending thoracic aortic aneurysm, p-value is calculated on annual coefficient change.

Particularly women had a slight increase in incidence of rupture repair, (Figure 16), driven by incidence of repair among younger women, Table 9.

The first patient to undergo a ruptured dTAA repair with TEVAR in this cohort was in year 2001. The proportion of TEVAR for rupture increased 1997-2003 to 2011-2017 from 12.7% to 86.4% (p<0.001) among ruptured dTAA repair. Among octogenarians, 95.5% was operated with TEVAR in the later time period (100% among women) and 83.3% in patients <80 years of age.

When assessing surgical outcome, no change in 90-days and 1-year mortality, nor long-term (5-years) survival after ruptured dTAA repair was seen during the study period, Figure 17 and Table 10.

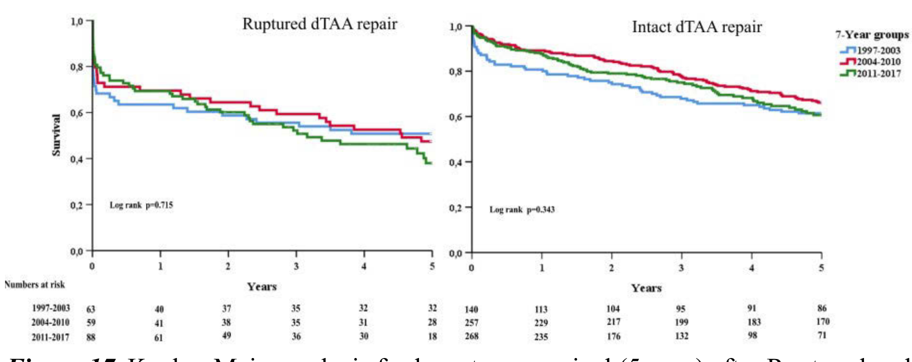

Figure 17. Kaplan-Meier analysis for long-term survival (5-year) after Ruptured and Intact descending thoracic aortic aneurysm repair.

Table 10. *Crude 90-days and 1-year mortality for patients undergoing ruptured or intact thoracic aortic repair 1997-2017 in Sweden. Overall and stratified by sex, age and surgical technique.*

		Intact dTAA repair				
		Total	**1997-2003**	**2004-2010**	**2011-2017**	**p-value**
90 days	**Mortality**	8.1% (54/665)	15.0% (21/140)	5.8% (15/257)	6.7% (18/268)	0.003
	Men	9.1% (39/427)	20.0% (18/90)	6.8% (11/162)	5.7% (10/175)	<0.001
	Women	6.3% (15/238)	6.0% (3/50)	4.2% (4/95)	8.6% (8/93)	0.462
	<80 years	7.9% (49/617)	15.3% (21/137)	5.8% (14/243)	5.9% (14/237)	0.001
	≥80 years	10.4% (5/48)	0.0% (0/3)	7.1% (1/14)	12.9% (4/31)	0.699
	OSR	10.2% (33/323)	14.6% (19/130)	6.2% (8/129)	9.4% (6/64)	0.080
	TEVAR	6.1% (21/342)	20.0% (2/10)	5.5% (7/128)	5.9% (12/204)	0.178
1 year	**Mortality**	13.2% (88/665)	19.3% (27/140)	10.9% (28/257)	12.3% (33/268)	0.053
	Men	14.5% (62/427)	23.3% (21/90)	10.5% (17/162)	13.7% (24/175)	0.020
	Women	10.9% (26/238)	12.0% (6/50)	11.6% (11/95)	9.7% (9/93)	0.883
	<80 years	12.5% (77/617)	19.7% (27/137)	9.9% (24243)	11.0% (26/237)	0.014
	≥80 years	22.9% (11/48)	0.0% (0/3)	28.6% (4/14)	22.6% (7/31)	0.563
	OSR	13.9% (45/323)	19.2% (25/130)	8.5% (11/129)	14.1% (9/64)	0.045
	TEVAR	12.6% (43/342)	20.0% (2/10)	13.3% (17/128)	11.8% (24/204)	0.711
		Ruptured dTAA repair				
		Total	**1997-2003**	**2004-2010**	**2011-2017**	**p-value**
90 days	**Mortality**	28.1% (59/210)	31.7% (20/63)	28.8% (17/59)	25.0% (22/88)	0.654
	Men	27.5% (36/131)	36.2% (17/47)	25.6% (10/39)	20.0% (9/45)	0.211
	Women	29.1% (23/79)	18.8% (3/16)	35.0% (7/20)	30.2% (13/43)	0.550
	<80 years	27.8% (47/169)	26.9% (14/52)	31.4% (16/51)	25.8% (17/66)	0.786
	≥80 years	29.3% (12/41)	54.5% (6/11)	12.5% (1/8)	22.7% (5/22)	0.085
	OSR	27.3% (24/88)	27.3% (15/55)	38.1% (8/21)	8.3% (1/12)	0.182
	TEVAR	28.7% (35/122)	62.5% (5/8)	23.7% (9/38)	27.6% (21/76)	0.083
1 year	**Mortality**	32.4% (68/210)	36.5% (23/63)	30.5% (18/59)	30.7% (27/88)	0.704
	Men	32.1% (42/131)	40.4% (19/47)	28.2% (11/39)	26.7% (12/45)	0.157
	Women	32.9% (26/79)	25.0% (4/16)	35.0% (7/20)	34.9% (15/43)	0.752
	<80 years	32.0% (54/169)	32.7% (17/52)	33.3% (17/51)	30.3% (20/66)	0.932
	≥80 years	34.1% (14/41)	54.5% (6/11)	12.5% (1/8)	31.8% (7/22)	0.153
	OSR	31.8% (28/88)	30.9% (17/55)	42.9% (9/21)	16.7% (2/12)	0.291
	TEVAR	32.8% (40/122)	75.0% (6/8)	23.7% (9/38)	32.9% (25/76)	0.019

TAA= thoracic aortic aneurysm, OSR= open surgical repair, TEVAR= thoracic endovascular aortic repair

When assessing predictors for short- and long-term mortality in a cox-regression analysis, increasing age and renal failure had a significantly raised hazard ratio, Table 11. In a Kaplan-Meier analysis there was no difference in long-term survival between men and women (47.3% and 48.8%, log-rank p=0.801).

Table 11. *Assessment of variables associated with postoperative (within 90-days) and long-term death (within 5-year) after thoracic aortic aneurysm repair in a multivariable Cox proportional hazard model.*

	Intact dTAA repair					
	90-days			5 year		
	HR	95.0% CI	p-value	HR	95.0% CI	p-value
Age. per year increase	1.04	1.00-1.07	0.030	1.05	1.03-1.07	<0.001
Men vs Women	1.49	0.82-2.71	0.194	1.10	0.84-1.46	0.481
OAR vs TEVAR	2.71	1.49-4.93	0.001	1.14	0.84-1.53	0.402
Cardiac disease	1.53	0.85-2.73	0.154	1.44	1.09-1.90	0.011
Pulmonary disease	2.23	1.25-3.96	0.006	1.70	1.27-2.28	<0.001
Cerebrovascular disease	0.59	0.21-1.66	0.316	0.78	0.50-1.24	0.296
Diabetes	1.37	0.63-2.95	0.425	1.09	0.74-1.62	0.661
Renal disease	1.98	0.99-3.97	0.055	1.65	1.15-2.36	0.006
	Ruptured dTAA repair					
	90-days			5 year		
	HR	95.0% CI	p-value	HR	95.0% CI	p-value
Age. per year increase	1.04	1.01-1.07	0.025	1.05	1.03-1.08	<0.001
Men vs Women	0.87	0.51-1.49	0.615	1.09	0.73-1.63	0.671
OAR vs TEVAR	1.25	0.71-2.21	0.431	0.99	0.65-1.52	0.961
Cardiac disease	0.84	0.49-1.44	0.522	0.91	0.62-1.35	0.651
Pulmonary disease	1.06	0.57-1.98	0.853	1.42	0.92-2.18	0.115
Cerebrovascular disease	1.43	0.64-3.20	0.389	0.78	0.39-1.55	0.469
Diabetes	0.61	0.24-1.58	0.313	1.07	0.59-1.93	0.832
Renal disease	2.04	1.06-3.92	0.033	2.14	1.31-3.49	0.002

dTAA= descending thoracic aortic aneurysm, OAR= OSR= open aortic/surgical repair, TEVAR= thoracic endovascular aortic repair, HR= hazard ratio, CI= confidence interval

The incidence of intact dTAA repair increased over time, with an annual increase in regression coefficient of 0.014 per 100.000 person-years; p=0.002, Figure 18.

The increasing incidence of intact dTAA repair was present both among men and women, (Figure 18 and Table 9). In the age-group, patients ≥80 years of age, there was an increase in incidence of intact dTAA repair with more than nine times during the study period, whilst the development was more modest among younger patients (Table 9). The first octogenarian to undergo repair for intact dTAA was in year 2000; in the last year of the study period 2017, patients' ≥80 years of age represented 12.5% of those who underwent repair for intact dTAA. With consistently increasing age of the operated patients, the proportion of patients with comorbidities (pulmonary, cerebrovascular, diabetes, renal) increased naturally over time (Table 8).

The first TEVAR for intact dTAA in this cohort was detected in 1999. During the following 21 years an increasing proportion of intact dTAA repairs were performed with TEVAR. The proportion intact dTAA repair increased 1997-2003 to 2011-2017 from 7.1% to 76.1% (p<0.001) (Table 8). Among octogenarians, 93.5% was operated with TEVAR in the last time period and 73.8% in patients <80 years of age. Of those <50 years of age undergoing intact dTAA repair, 15.4% underwent TEVAR over the full study period.

The 90-days mortality after intact dTAA repair decreased overall (Table 10). The improvement in perioperative outcome was significant among men, but not among women, and was sustained at 1-year in men (Table 10). Mortality was lower after TEVAR (6.1%) when compared to OSR (10.2%, p=0.048), despite that TEVAR patients were older (mean age TEVAR 72.0 years, OSR 65.0 years, p<0.001). One year survival was equal for TEVAR and OSR. The 5-year survival rate did not change over time, (Figure 17).

In a cox-proportional hazard model, open repair was associated with a 2.7 hazard ratio (HR) for perioperative death compared to TEVAR, Table 11. Increasing age and pulmonary disease proved to be predictors of higher perioperative mortality. In the long-term, increasing age, cardiac, pulmonary and renal comorbidities were associated with higher HR for death, whilst surgical technique was not. Sex was not associated with postoperative death neither in short- (Table 11) nor long-term (men 65.8% and women 66.8%, p=0.709).

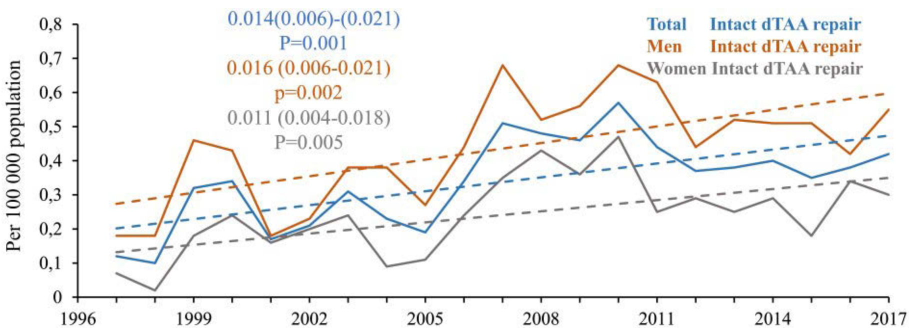

Figure 18. Incidence of intact descending thoracic aortic aneurysm repair per 100,000 population, in total, men and women (coefficient, 95% CI and P-value).

Discussion

During the last 25 years, the management of AA and RAA has undergone great changes in Sweden with a launch of an AAA screening program, improved emergency medical services, increased availability and use of imaging (ultrasound, computed tomography, and magnetic resonance imaging) in medical practice, broad introduction of endovascular solutions (EVAR/TEVAR) and improved surgical care [51, 134, 135]. In addition, previous reports have indicated a decreasing prevalence of aortic aneurysms in Sweden, mainly as a result of reduced smoking exposure [134], this is also reflected in an overall decreasing incidence of RAAA (study II). The change in incidence of RAAA displays a difference between men and women, although smoking habits have improved equally in both sexes [136]. While incidence of RAAA decreased among men, women had a relatively stable incidence of RAAA over time. This difference of incidence reduction in RAAA between the sexes may partly be explained by the screening program which started in 2006 and focuses on men >65 years of age.

The overall short- and long-term mortality after RAAA repair is also improving (study II and study III) over time mainly due to: 1) an increasing proportion of RAAA patients presenting to hospital facility alive, 2) an increasing proportion of ruptured aortic aneurysm being operated on, and 3) improved surgical outcome due to increasing use of EVAR.

These findings are supported by previous reports from Finland and England [3, 38, 100]. Although women have improved survival after RAAA over time, there is a sex difference also in post RAAA survival, with women having a poorer survival rate. This is because a lower proportion of women are operated on, especially women >80 years of age, but also because of an inferior surgical outcome compered to elderly men since woman had a lower rate of EVAR. However, the improvement in outcome for patients with rupture of the descending thoracic aorta was not achieved despite the fact that the transition from OSR to TEVAR has been even more radical for treatment of this diagnosis (study IV). These results may be explained by the fact that an increasing number of octogenarians and patients with a higher burden of comorbidities are offered surgery while the aneurysm is still intact, with improved surgical results. This has led to fewer RdTAA presenting to hospitals and hence the incidence of RdTAA repairs has decreased, whilst the opposite goes for intact dTAA.

Study I found that three referral vascular centres in Sweden had developed a distinct primary EVAR strategy for treatment of ruptures during the study period, treating more than 50% of all RAAA repairs with EVAR. Fourteen other centres used EVAR in a more modest frequency. This is a moving target, and over time the number of centres with a primary EVAR strategy for ruptures has increased in Sweden, as reflected in the recent Swedvasc annual report [91]. Overall, EVAR was the method of choice in 40% of all RAAA operated and 60% of RAAA operations on octogenarians in 2013 (study II). The first recorded endovascular repair on RAAA was in this material in 1995 (study II), on intact dTAA in 1999 and on RdTAA in 2001 (study IV), indicating that during this time span of almost 25 years that is covered in this thesis, important technical development and logistical changes have occurred in the overall management of RAA.

In Study I, no difference in 30- days, 1 and 2 years mortality between primary open and endovascular strategies for RAAA was detected, suggesting that the strategies are equivalent without any inferiority. The RCTs that have been conducted comparing EVAR with OSR for RAAA, have not been able to demonstrate any early survival benefit for EVAR, supporting the findings in study I [96, 97, 103, 104].

The improved perioperative outcome after EVAR seen in retrospective studies has been described as due to selection bias. In study I, when assessing the surgical techniques and not strategy there was in fact lower peri-operative mortality for patients selected for EVAR, in line with previous population and centre based reports [55, 98, 137].

Referrals are a much debated confounder when assessing survival after ruptured aortic surgery. It is anticipated that patients referred from a district general hospital with a vascular surgical service to a tertiary referral centre are more complex patients, with a potentially poorer outcome. On the other hand, patients with aortic rupture who survive the transfer period for treatment at a tertiary referral centre are probably more stable than those treated at the presenting hospital, suggesting a potential for better outcome for referred patients. In study I, the referral rate was higher at hospitals with a primary EVAR strategy and therefore data was analysed with the referral cases excluded, this however did not affect the result. Study I showed that patients referred for endovascular repair to primary EVAR centres had a tendency towards better survival despite the fact that these were often high risk patients, deemed unfit for open repair.

The IMPROVE trial (the largest RCT-trial on RAAA), with a similar set up to study I in assessing surgical strategy and not technique, detected an advantage for EVAR in survival after 3-years [100], suggesting convincing support for the benefits of an endovascular strategy versus open repair to treat patients with ruptured abdominal aortic aneurysm. This result was a breakthrough for RCT´s in being able to show advantages of EVAR as treatment for RAAA.

The up-to-date European guideline on management of abdominal aortic aneurysm, after scrutinizing the literature, recommends EVAR [101] as the primary procedural option if the patients with RAAA have suitable anatomy.

In addition to improved mid-term survival, EVAR for RAAA introduces other benefits for patients suffering from aortic rupture. The IMPROVE trial also showed that patients treated with EVAR had a higher chance of being discharged to home at an earlier date compared to those undergoing OSR for RAAA [100]. Returning to independent life after any type of surgical treatment is an extremely important aspect for patients. In study I, centres with a high rate of EVAR, treated a significantly larger proportion of patients with pulmonary comorbidities and they could also reduce massive bleeding. Further, study II suggests that, over time, a more frequent use of EVAR for treatment of RAAA resulted in more intervention in elderly patients with rupture, leading to a higher proportion of RAAA patients with rupture being offered surgical treatment and undergoing repair. This trend occurred without any deterioration in surgical outcome (90-day mortality rate) – on the contrary, an improvement in survival after RAAA repair could be seen. This was more clearly demonstrated after adjusting surgical outcome for increasing use of endovascular repair over time. The analysis suggests that EVAR has had a major impact on the improving surgical results of RAAA treatment in Sweden over time.

The increasing implementation of EVAR as first-line strategy for management of RAAA has mainly been driven by the reduction in peri-operative mortality rates [51, 138, 139]. However, whether or not the early survival advantage is maintained over time has been a matter for debate. The results in Study III, demonstrate that the improved surgical outcome from study II was converted into improved long-term survival over time in contrast to a previous report from Sweden, showing an unchanged long-term survival after RAAA repair 1987-2005 [140]. Findings in the current study are also in line with contemporary studies such as a report from Vascular Quality Initiative registry 2020, where the conclusion is that early benefits of EVAR are sustained over time [141]. In study III, patients who had undergone surgery up until 2018 were added to the cohort from study II. Study III displayed that the RAAA treated population continued progressively to contain more and more women, octogenarians, patients with multiple comorbidities as well as EVAR became increasingly dominant as the treatment strategy.

The number of individuals with RAAA presenting to hospitals also continued to decline over the additional four years that study III spanned. The reason is a continued decrease in the prevalence of aortic disease due to reduced smoking and improved management of cardiovascular risk factors [39, 134], which in turn has resulted in a reduction in the incidence of RAAA. An additional explanation is that the nationwide AAA screening program likely plays an important role. The screening program did not reach national coverage until

2015, therefore the full effect of screening had not been reached during the period of study II and probably did not reached full effect even during the extended study period in study III.

The last period (2010-2017) in study III were significantly associated with reduced odds of overall mortality. Long-term survival improved throughout the study timeframe due to the fact that EVAR was associated with reduced hazard of long-term mortality and that proportion of EVAR increased, 1.5% in the first time period (1994-2001) to 35.5% in the last. The reduction of 90-day mortality after repair from Study II, persisted in study III despite the fact that the operated patients generally became older and more fragile. In a Cox regression analysis, EVAR was an independent negative predictor for 90-day mortality. When comparing surgical approach, a reduction in unadjusted long-term survival was noticed in the latter time period among patients undergoing EVAR. The most likely explanations to this are firstly, the massive selection bias between the time periods (only 52 out of 3418 operations was EVAR during the first time period) and secondly, the change in patients characteristics over time. The findings clearly support an EVAR-first policy in suitable candidates for acute management of RAAA, in line with prevailing European guidelines.

Further explanations to the improved long-time survival is, despite increasing comorbidity, that prevention and treatment of the most common causes of fatal diseases in Sweden has improved during the 24 years that study III covers. The incidence and mortality from heart attacks has decreased in Sweden by approximately 36% and 56% respectively and 5-year survival after a cancer diagnose improved by >20% from 2000 to 2015 [85, 142]. Despite this, cardiovascular diseases accounted alone for one third, and together with cancer, for more than 50% of late cases of death (>90-days survival), in study III, even though late death due to cardiovascular diseases decreased slightly. Both cardiovascular pathology and cancer are age-related [143] and as more, older patients were offered repair and survived their RAA, their prevalence in the study cohort naturally increase. This of course could impact the results in study IV included in this thesis as well.

In order to gain an increased understanding for endovascular surgery of ruptured aortic aneurysm, study IV assessed trends in epidemiology and outcome on surgically treated descending thoracic aortic aneurysms (dTAA) over a time span of 21 years in Sweden. An interesting aspect of the study was the introduction of TEVAR as treatment for intact and ruptured dTAA started approximately 5 years after the introduction of EVAR as treatment for AAA in Sweden. The implementation and establishment of TEVAR has been much more progressive in comparison. Study IV concluded that: 1) The incidence of ruptured dTAA repair was stable, and no significant improvement in outcome was achieved in patients with dTAA rupture undergoing repair; 2) The incidence of intact dTAA repair increased, mainly due to the fact that more surgery was performed on male octogenarians; 3) TEVAR has become the surgical method that is primarily used in the operation for both intact and ruptured dTAA. This has resulted in an improved short- and medium-term mortality after intact dTAA repair in men, despite an increase in octogenarians with escalating comorbidity among the treated patients over time. However, long-term survival is unchanged. These findings confirm that the broad introduction of TEVAR as primary technique for intact dTAA repair has resulted in a change in indication for treatment, with an increasing number of patients being offered surgery, especially among the elderly, with improved perioperative outcome [144]. Nonetheless, in this material, it seems that today's surgeons' need for OSR remains, especially among younger patients, probably due to inappropriate anatomy for TEVAR and the knowledge that exists with endografts in the aorta and long-term complications. The observed increase in surgical activity in Sweden is in line with a recent report from Germany [62] which reported a 100% increase in the number of dTAA operations and a 70% increase in incidence of dTAAs operated on during the last decade. Study IV could not observe any significant change in incidence of dTAA rupture repair. Although it would have been plausible to detect a reduction in number of ruptures based on the increase in intact dTAA repair activity, it should be noted that the current study only evaluated patients undergoing surgical treatment for rupture; hence any changes in rupture incidence, as well as in proportion of dTAA ruptures being offered surgical intervention, would affect these results. It is interesting to note that whilst the male:female ratio among patients undergoing ruptured dTAA repair was 4.5:1 early in this study period (1997-2003), it was equalised to 1:1 in the final study period (2011-2017). Whether this change is due to an increasing prevalence of rupture in women, or increasing proportion of women with rupture being offered surgical treatment cannot be assessed in the current dataset.

The overall short-term mortality after intact dTAA repair was 6.7% in the final time period and 5.9% among those who were repaired by TEVAR. These results are on par with a study on 9518 patients from 13 countries [145] where short-term mortality was 4.9% after TEVAR. Similar data were presented from a meta-analysis [146] that reported a short-term mortality of 4.4% after TEVAR. In contrast to study IV, most previous studies on outcome after TEVAR are not population-based (based on either registries or centre-based report), introducing the risk for selection bias affecting outcome.

The current analysis found an improvement in early mortality after intact dTAA repair, mainly due to decreasing mortality among men. Interestingly, mortality among men undergoing intact dTAA repair in the first time period was very high at 20.0% (much higher than what was observed in women), and reduced to 5.7% in the final time period. Overall, the improvement in short-term and mid-term mortality is partly attributed the increased use of TEVAR with improved outcome. When assessing early mortality after intact dTAA repair, OSR was the strongest predictor of early mortality, with a hazard ratio of 2.7. However, surgical technique did not affect long-term survival in this analysis.

Despite the improvement in short term outcome after intact dTAA repair over time, long-term survival was unchanged. This finding should be interpreted in the context of patients being treated in the final time period being significantly older and with higher rate of comorbidities than those operated early on. The long-term survival rate of 66.2% at 5-years after intact dTAA repair is in line with previous reports [147, 148], and similar or even lower than what has been reported at 5-years after intact abdominal aortic aneurysm repair at approximately 65-70% [140, 149, 150]. The causes of long-term mortality were not assessed in study IV, yet it is known that patients with aortic disease have an increased cardiovascular mortality compared to general population as earlier discussed, and improved secondary cardiovascular care as well as post-surgery surveillance may be important factors that may contribute to improvement in long-term outcome.

There are some logistical challenges in using an endovascular (EVAR and TEVAR) approach as treatment of aortic rupture in an acute setting. For instance, there must be an operating theatre with the possibility to use a fluoroscope suitable for the purpose with a 24-hour availability. Vascular surgeons or interventionists with knowledge of the procedure must also be available at all times, backed up by surgical nurses who are familiar with endovascular techniques. For hospitals that do not have a hybrid theatre and staff in place, a development towards being able to perform endovascular "around the clock" solutions is associated with major financial development costs for technology investment and staff training. With this in mind, the possibility of being treated with endovascular methods thus increases if the patients are treated in a teaching hospital or vascular centre where such investments were done decades ago, giving rise to a risk of the inherent selection bias for endovascular versus open treatment in studies. As the progressive adoption of EVAR as strategy for emergent management of RAA has continued, it is also reasonable to assume that over time EVAR was progressively adopted even outside the endografts instructions-for-use, a factor which could also impact outcomes of treatment.

Limitations

Studies in this thesis are based on registry data, which have both limitations and benefits. The benefits of population based studies include the non-selective patient cohort, which reflects contemporary "real world" practice and outcome. The unique personal identification number that all Swedish citizens obtain enables cross-matching of registries and national administrative databases could therefore be combined with a vascular surgical quality registry for national analysis in a uniform, single provider health care system such as the Swedish. This created the possibility to conduct national analysis of data. The national registries (NPR and CDR) suffer from the risk for misclassifications of disease in the coding. However, in study II, there was an excellent overlap between Swedvasc and NPR in terms of patients undergoing aortic repair, indicating adequate registration. While coding errors are still possible, such errors would affect study groups equally, as data collection occurred independently from scientific enquiries as our investigation. The rate of misclassification can also be affected by the AAA screening program. There is a paradox in the effect of AAA screening on incidence of RAAA as reported in registries. If a patient with a known AAA dies a sudden death, the chance that the cause of death is registered as RAAA is presumably greater than if the AAA is unknown at the time of death. Thus, AAA screening may result in an increase in the administrative registration of deaths due to RAAA, although the true trend may be the opposite.

The autopsy rate in Sweden during the period of studies ranged from 12% to 6 %. This increases the risk for sudden deaths due to RAAA being misclassified in the CDR as cardiac deaths, and this may affect calculation of RAA incidences in the studies. Data regarding survival was nearly complete with almost no loss to follow-up thanks to the possibility to cross match all cases with the Swedish population registry using a unique identification number for all study subjects. The only loss to follow-up for survival analysis in the current studies would be emigration from Sweden. The annual proportion of emigrants was stable over time, with average yearly rates that were estimated at 0.07% (±0.02%) for those aged >70 years and 0.16% (±0.03%) for those aged >50 years, based on national statistics. Therefore, it is unlikely that loss to follow-up could have affected the overall trends analysed in the current studies.

Conclusions

There was no difference in mortality outcome after RAAA repair among centres with a primary EVAR strategy compared with primary OSR strategy. Patients treated with EVAR had a lower mortality at 30 days, regardless of strategy.

During two decades (1994-2013), the total mortality due to RAAA decreased in Sweden. This was driven by a falling incidence of the disease, an increasing proportion of patients with RAAA reaching hospital alive and undergoing repair, as well as a steadily improving survival after RAAA repair. While the results are improving in men, RAAA incidence was stable in women and mortality after RAAA was higher in women than in men.

The long-term survival has improved in Sweden after RAAA repair during 24 years (1994-2017) mainly explained by improved perioperative survival over time. This is despite changes in the treatment strategy and that the operated patients generally became older and more fragile.

The incidence of intact dTAA repair increased in Sweden 1997-2017, mainly due to broad introduction of TEVAR and repairs being performed in elderly patients. Early mortality among men who underwent intact dTAA repair decreased despite an increasing proportion of those undergoing repair being ≥80 years of age and with more comorbidities. No change in outcome after repair could be detected among female patients over these 21 years. Long-term survival remained stable over time after both intact and ruptured dTAA repair.

Future research perspectives

The findings in this thesis support that RAA mortality in Sweden has decreased since the mid-90s. Whilst this reduction is multifactorial, it is partly due to the gradual introduction of endovascular techniques. However, the studies also conclude that OSR has a continuing role in the treatment of RAA. What the future holds is difficult to predict; for now, studies which help to tailor the optimal surgical strategy to the right individual for the optimal result would be valuable. The attitude that the different approaches in the treatment of AA and ruptures should not compete against each other, but cooperate is of value.

Although much has happened around the care of aortic rupture and the results are improving in men, ruptured AAA incidence is stable in women, and aortic rupture is associated with a higher mortality than in men. This indicates a need for focused efforts to improve the results of this fatal disease in women. Further research investigating the reasons for the worse outcome of RAAA in women is warranted.

The causes of long-term mortality was not assessed in this thesis. It is known that patients with aortic disease have an increased cardiovascular mortality compared to general population. Based on that knowledge, secondary cardiovascular care as well as improved surveillance post-surgery may be important factors that may contribute to improvement in long-term outcome and merit further studies. A tailored follow-up protocol centred on secondary prevention and management of cardiovascular conditions could be valuable but needs to be defined and evaluated.

In the contemporary era more focus needs to be on the long-term durability of EVAR procedures and their overall cost-effectiveness. Whether EVAR or TEVAR in the setting of RAA with unsuitable or unfavourable anatomy, forcing surgeons to go outside the endografts instructions-for-use, should still be regarded as the preferred management option, as compared to OSR or more complex endovascular techniques, remains a question to be addressed in future research.

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You all, are more than I could ever wish for.

Populärvetenskaplig sammanfattning (Summery in Swedish)

Stora kroppspulsådern (aortan) är det blodkärl som leder blodet från hjärtat ut till kroppens alla organ och delar. Aortaaneurysm (AA), en sjuklig utvidgning (bråck), är den vanligaste sjukdomen som drabbar kroppspulsådern och kan uppstå var som helst under dess ”förlopp”. AA uppstår vanligtvis i den delen som sitter i buken och benämns då abdominellt AA (AAA). AAA är en relativt vanlig sjukdom, den förekommer hos ca 1.5 % av alla 65-åriga män och hos ca 0.5 % av alla 70-åriga kvinnor i Sverige. Risken med aneurysmen är att de tillväxer med åren och till slut spricker (rupturerar) med katastrofala följder. För den som drabbas av aortaruptur (RAA) är det endast en akut operation som kan rädda livet och uppskattningsvis utgör aortaruptur 1 % av dödsorsakerna bland avlidna män över 60 års ålder i Sverige. Med målet att förhindra ruptur, har riktlinjer utvecklats för att identifiera patienter i riskzonen och operera dessa aneurysm i tid. Av de som drabbas av en aortaruptur hinner inte ens hälften ta sig in till sjukhus för att bli opererade medan de som klarar transporten in och snabbt får möjlighet till kirurgisk behandling har en relativt god chans att överleva. Det finns idag två olika operationsmetoder att tillgå. Den klassiskt traditionella metoden är en öppen aorta operation (OSR) där den sjuka eller rupturerade delen av kroppspulsådern ersätts med ett konstgjort kärl som sys in. Det är ett stort kirurgiskt ingrepp som kräver att patienten är i full narkos, vilket i sig är ett riskfullt tillstånd för patienter i cirkulatorisk svikt, som exempelvis en ruptur. Den andra, en mer modern metod, är en teknik där man istället lagar aortan genom att gå in med tätningsmaterial (stentgraft) genom patientens ljumsk-kärl och på så sätt placerar in ett konstgjort kärl som förstärker och vid ruptur tätar, den sjuka delen av aortan. Den sistnämnda metoden kallas för endovaskulär aorta reparation (EVAR) och är en minimalinvasiv operation som kan utföras på en vaken patient i lokalbedövning. Eftersom EVAR är mycket mindre traumatisk och innebär en mindre fysiologisk påverkan kan allt äldre och sjukare patienter erbjudas operation, vilket gäller både elektivt intakta aneurysm och de som rupturerat. Utvecklingen av EVAR har lett till att även den del av kroppspulsådern som sitter i bröstkorgen nu går att opereras minimi-invasivt, det benämns då thorakal EVAR (TEVAR).

Syftet med denna avhandling var att studera trender inom epidemiologi och behandling av aortaaneurysm samt resultaten av kirurgisk åtgärd med särskilt fokus på aortarupturer.

I **delarbete I** analyserades om EVAR som primär strategi för behandling av rupturerade abdominala AA (RAAA) hade påverkat det kirurgiska resultatet. Alla patienter som opererades i Sverige mellan maj 2008 till december 2012 och som registrerats i det svenska kärlregistret Swedvasc ingick i analysen. Totalt inkluderades 1304 patienter från 29 olika sjukhus som har kärlkirurgi i ordinarie verksamhet. Sjukhus med en primär EVAR -strategi (behandling >50 % av RAAA med EVAR) jämfördes med sjukhus som hade en primär öppen kirurgisk strategi (behandling <50 % av RAAA med EVAR).

Resultatet av analysen visade ingen skillnad mellan strategierna avseende dödligheten efter operation av RAAA varken inom 30- dagar eller efter 1 respektive 2 år. Dock hade EVAR som metod, sammantaget alla sjukhusens EVAR operationer, en minskad dödlighet i samband med att patienterna opererades (död inom 30-dagar efter operationen).

I **delarbete II** var avsikten att få en uppdatering av epidemiologin samt analysera resultatet efter behandling av RAAA, i skenet av ett modernare omhändertagande av patienter med AAA. Syftet var även att utvärdera effekten av en gradvis ökande tillämpning av EVAR som operationsmetod. Alla patienter i Sverige som drabbats av RAAA (vårdats, opererats, dött eller på något annat sätt varit i kontakt med sjukvården och fått diagnosen RAAA) under en period av 20 år, 1994 till 2013, inkluderades. Totalt 18766 individer med diagnosen RAAA identifierades från dödsorsaks-registret, patientregistret och Swedvasc. Tiden för studien delades in i fyra 5-års grupper (grupp 1, 1994-1998, grupp 2, 1999-2003, grupp 3, 2004-2008, grupp 4, 2009-2013) för att kunna analysera förändringar över tid.

Denna analys visade att dödligheten till följd av RAAA i Sverige minskade över tid, framförallt bland män. Den minskade dödligheten beror på en successiv minskning av antal RAAA mellan 1994 till 2013. Andra orsaker till att dödligheten i RAAA sjönk under studien vara att allt fler som drabbades av aortaruptur överlevde till sjukhus och blev opererade. Operationsmetoden EVAR användes i ökande grad med resultatet att fler patienter överlevde operationen.

Delarbete III är en fortsättning av delarbete II men med fokus på de som blivit opererade för ett RAAA. Här analyserades lång-tids överlevnad (5 år) mot bakgrund av att allt färre patienter blir opererade med klassisk öppen kirurgi och allt fler med EVAR. Till delarbete III gjordes ett utökat registeruttag av data för att förlänga studieperioden med 4 år till totalt 24 år (1994-2017), detta för att inkludera patienter som blev opererade till och med 2017. Totalt 8928 individer som blivit opererade på grund av ett RAAA identifierades från patientregistret och svenska kärlkirurgiska registret Swedvasc. Uppdelningar avseende ålder och kön gjordes, som i delarbete II för olika analyser, men nu i tre 8-årsperioderm istället.

Resultaten av analyserna visade att långtidsöverlevnaden efter operation av RAAA förbättrats från 1994 till 2017. Främst förklaras detta av en allt bättre överlevnad i samband med det akuta kirurgiska ingreppet, detta trots att de som opererats blivit gradvis äldre och sjukare.

I **delarbete IV** analyserades alla individer som opererat ett aneurysm i den delen av aortan som är beläget i bröstkorgen (thorax), närmare bestämt den nedåtgående (descenderande) delen av torakal-aortan (dTAA). Individerna delades upp mellan de som blivit opererade innan (intakt aneurysm) eller efter att aneurysmet rupturerat för att analysera och bedöma hur incidensen och det kirurgiska resultatet av dTAA kirurgi förändrats från 1997 till 2017 (21 år). 875 individer som blivit opererade på grund av dTAA identifierades från patient och dödsorsaksregistret, 665 intakta och 210 rupturerade dTAA.

Analyserna visade att den tidiga dödligheten (död inom 30 dagar) efter operation av intakta dTAA minskade för män under studieperioden, trots att andelen opererade över 80 års ålder ökade. Antalet opererade intakta dTAA per 100000 invånare (Incidensen) i Sverige ökade främst på grund av att TEVAR under studieperioden infördes och med det kunde äldre och sjukare patienter erbjudas operation för sitt dTAA. För kvinnor däremot kunde ingen förändring ses avseende resultaten efter operation av intakta dTAA och detsamma gällde överlevnaden efter operation av samtliga rupturerade dTAA (RdTAA)patienter. Långtidsöverlevnaden förblev stabil efter operation av både intakta och rupturerade dTAA över studietiden.

Sammanfattningsvis har dagens moderna sätt att handlägga aortaaneurysm, med nya endovaskulära metoder, resulterat i en betydande förändring av hur patienter med RAA och dTAA omhändertas och behandlas i Sverige. De omfattande (ovan nämnda) rikstäckande befolkningsbaserade registerstudierna i den här avhandlingen pekar på att EVAR/TEVAR har resulterat i en förbättrad överlevnad för patienter som drabbats av RAAA samt att resultaten efter operation av dTAA har förbättrats.

References

1. Gunnarsson K, Wanhainen A, Björck M, Djavani-Gidlund K, Mani K. Nationwide Study of Ruptured Abdominal Aortic Aneurysms During Twenty Years (1994-2013). *Ann Surg* 2021; 274(2):e160-e166.
2. Bengtsson H, Bergqvist D. Ruptured abdominal aortic aneurysm: a population-based study. *J Vasc Surg* 1993; 18(1):74-80.
3. Laine MT, Laukontaus SJ, Sund R, Aho PS, Kantonen I, Alback A, Venermo M. A Population-Based Study of Abdominal Aortic Aneurysm Treatment in Finland 2000 to 2014. *Circulation* 2017; 136(18):1726-1734.
4. Johansson G, Markström U, Swedenborg J. Ruptured thoracic aortic aneurysms: a study of incidence and mortality rates. *J Vasc Surg* 1995; 21(6):985-8.
5. Sterpetti AV, Schultz RD, Feldhaus RJ, Cheng SE, Peetz DJ, Jr. Factors influencing enlargement rate of small abdominal aortic aneurysms. *J Surg Res* 1987; 43(3):211-9.
6. Johnston KW, Rutherford RB, Tilson MD, Shah DM, Hollier L, Stanley JC. Suggested standards for reporting on arterial aneurysms. Subcommittee on Reporting Standards for Arterial Aneurysms, Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery and North American Chapter, International Society for Cardiovascular Surgery. *J Vasc Surg* 1991; 13(3):452-8.
7. McGregor JC, Pollock JG, Anton HC. The value of ultrasonography in the diagnosis of abdominal aortic aneurysm. *Scott Med J* 1975; 20(3):133-7.
8. Hannuksela M, Lundqvist S, Carlberg B. Thoracic aorta--dilated or not? *Scand Cardiovasc J* 2006; 40(3):175-8.
9. G. M. Etymological dictionary of the new Greek Language: the history of the words., 2009.
10. Antoniou GA, Antoniou AI, Antoniou SA, Lazarides MK. A historical perspective of medical terminology of aortic aneurysm. *J Vasc Surg* 2011; 54(5):1527-8.
11. Ghalioungui P. Magic and medical science in ancient Egypt. London: Hodder and Stoughton, 1963.
12. Friedman SG, Friedman MS. Matas, Antyllus, and endoaneurysmorrhaphy. *Surgery* 1989; 105(6):761-3.
13. Fortner G, Johansen K. Abdominal aortic aneurysms. *West J Med* 1984; 140(1):50-9.
14. Thompson JE. Early history of aortic surgery. *J Vasc Surg* 1998; 28(4):746-52.
15. Dubost C, Allary M, Oeconomos N. Resection of an aneurysm of the abdominal aorta: reestablishment of the continuity by a preserved human arterial graft, with result after five months. *AMA Arch Surg* 1952; 64(3):405-8.

16. Freeman ME, Leeds FH. Vein inlay graft in the treatment of aneurysms and thrombosis of the abdominal aorta; a preliminary communication with report of 3 cases. *Angiology* 1951; 2(6):579-87.
17. Bahnson HT. Considerations in the excision of aortic aneurysms. *Ann Surg* 1953; 138(3):377-86.
18. Voorhees AB, Jr., Jaretzki A, 3rd, Blakemore AH. The use of tubes constructed from vinyon "N" cloth in bridging arterial defects. *Ann Surg* 1952; 135(3):332-6.
19. De Bakey ME, Cooley DA, Crawford ES, Morris GC, Jr. Clinical application of a new flexible knitted dacron arterial substitute. *Am Surg* 1958; 24(12):862-9.
20. Donald I, Macvicar J, Brown TG. Investigation of abdominal masses by pulsed ultrasound. *Lancet* 1958; 1(7032):1188-95.
21. Volodos NL, Shekhanin VE, Karpovich IP, Troian VI, Gur'ev Iu A. [A self-fixing synthetic blood vessel endoprosthesis]. *Vestn Khir Im I I Grek* 1986; 137(11):123-5.
22. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. *Ann Vasc Surg* 1991; 5(6):491-9.
23. Yusuf SW, Whitaker SC, Chuter TA, Wenham PW, Hopkinson BR. Emergency endovascular repair of leaking aortic aneurysm. *Lancet* 1994; 344(8937):1645.
24. Semba CP, Kato N, Kee ST, Lee GK, Mitchell RS, Miller DC, Dake MD. Acute rupture of the descending thoracic aorta: repair with use of endovascular stent-grafts. *J Vasc Interv Radiol* 1997; 8(3):337-42.
25. Jacomelli J, Summers L, Stevenson A, Lees T, Earnshaw JJ. Impact of the first 5 years of a national abdominal aortic aneurysm screening programme. *Br J Surg* 2016; 103(9):1125-31.
26. Ailawadi G, Eliason JL, Upchurch GR, Jr. Current concepts in the pathogenesis of abdominal aortic aneurysm. *J Vasc Surg* 2003; 38(3):584-8.
27. Albornoz G, Coady MA, Roberts M, Davies RR, Tranquilli M, Rizzo JA, Elefteriades JA. Familial thoracic aortic aneurysms and dissections--incidence, modes of inheritance, and phenotypic patterns. *Ann Thorac Surg* 2006; 82(4):1400-5.
28. Bengtsson H, Bergqvist D, Sternby NH. Increasing prevalence of abdominal aortic aneurysms. A necropsy study. *Eur J Surg* 1992; 158(1):19-23.
29. Central Bureau of Statistics (SCB) S. Statistics on causes of death 2017-Autopsy rate 1987-2017. 2018.
30. Lederle FA, Johnson GR, Wilson SE, Chute EP, Hye RJ, Makaroun MS, Barone GW, Bandyk D, Moneta GL, Makhoul RG. The aneurysm detection and management study screening program: validation cohort and final results. Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. *Arch Intern Med* 2000; 160(10):1425-30.
31. Ashton HA, Buxton MJ, Day NE, Kim LG, Marteau TM, Scott RA, Thompson SG, Walker NM. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. *Lancet* 2002; 360(9345):1531-9.
32. Lindholt JS, Juul S, Fasting H, Henneberg EW. Screening for abdominal aortic aneurysms: single centre randomised controlled trial. *Bmj* 2005; 330(7494):750.

33. Kent KC, Zwolak RM, Egorova NN, Riles TS, Manganaro A, Moskowitz AJ, Gelijns AC, Greco G. Analysis of risk factors for abdominal aortic aneurysm in a cohort of more than 3 million individuals. *J Vasc Surg* 2010; 52(3):539-48.
34. Programme NAAAS. The NHS abdominal aortic aneurysm screening report 2014.
35. Wanhainen A, Hultgren R, Linne A, Holst J, Gottsäter A, Langenskiöld M, Smidfelt K, Björck M, Svensjö S, Swedish Aneurysm Screening Study G. Outcome of the Swedish Nationwide Abdominal Aortic Aneurysm Screening Program. *Circulation* 2016; 134(16):1141-1148.
36. Thompson SG, Bown MJ, Glover MJ, Jones E, Masconi KL, Michaels JA, Powell JT, Ulug P, Sweeting MJ. Screening women aged 65 years or over for abdominal aortic aneurysm: a modelling study and health economic evaluation. *Health Technol Assess* 2018; 22(43):1-142.
37. Svensjö S, Björck M, Wanhainen A. Current prevalence of abdominal aortic aneurysm in 70-year-old women. *Br J Surg* 2013; 100(3):367-72.
38. Anjum A, von Allmen R, Greenhalgh R, Powell JT. Explaining the decrease in mortality from abdominal aortic aneurysm rupture. *Br J Surg* 2012; 99(5):637-45.
39. Persson SE, Boman K, Wanhainen A, Carlberg B, Arnerlov C. Decreasing prevalence of abdominal aortic aneurysm and changes in cardiovascular risk factors. *J Vasc Surg* 2017; 65(3):651-658.
40. Svensjö S, Bengtsson H, Bergqvist D. Thoracic and thoracoabdominal aortic aneurysm and dissection: an investigation based on autopsy. *Br J Surg* 1996; 83(1):68-71.
41. Bickerstaff LK, Pairolero PC, Hollier LH, Melton LJ, Van Peenen HJ, Cherry KJ, Joyce JW, Lie JT. Thoracic aortic aneurysms: a population-based study. *Surgery* 1982; 92(6):1103-8.
42. Clouse WD, Hallett JW, Jr., Schaff HV, Gayari MM, Ilstrup DM, Melton LJ, 3rd. Improved prognosis of thoracic aortic aneurysms: a population-based study. *JAMA* 1998; 280(22):1926-9.
43. Itani Y, Watanabe S, Masuda Y, Hanamura K, Asakura K, Sone S, Sunami Y, Miyamoto T. Measurement of aortic diameters and detection of asymptomatic aortic aneurysms in a mass screening program using a mobile helical computed tomography unit. *Heart Vessels* 2002; 16(2):42-5.
44. Choksy SA, Wilmink AB, Quick CR. Ruptured abdominal aortic aneurysm in the Huntingdon district: a 10-year experience. *Ann R Coll Surg Engl* 1999; 81(1):27-31.
45. Acosta S, Ögren M, Bengtsson H, Bergqvist D, Lindblad B, Zdanowski Z. Increasing incidence of ruptured abdominal aortic aneurysm: a population-based study. *J Vasc Surg* 2006; 44(2):237-43.
46. Lederle FA, Wilson SE, Johnson GR, Reinke DB, Littooy FN, Acher CW, Ballard DJ, Messina LM, Gordon IL, Chute EP, Krupski WC, Busuttil SJ, Barone GW, Sparks S, Graham LM, Rapp JH, Makaroun MS, Moneta GL, Cambria RA, Makhoul RG, Eton D, Ansel HJ, Freischlag JA, Bandyk D. Immediate repair compared with surveillance of small abdominal aortic aneurysms. *N Engl J Med* 2002; 346(19):1437-44.

47. The UK Small Aneurysm Trial Participants. Long-term outcomes of immediate repair compared with surveillance of small abdominal aortic aneurysms. *N Engl J Med* 2002; 346(19):1445-52.
48. Wilmink AB, Quick CR. Epidemiology and potential for prevention of abdominal aortic aneurysm. *Br J Surg* 1998; 85(2):155-62.
49. Mureebe L, Egorova N, Giacovelli JK, Gelijns A, Kent KC, McKinsey JF. National trends in the repair of ruptured abdominal aortic aneurysms. *J Vasc Surg* 2008.
50. Otterhag SN, Gottsäter A, Lindblad B, Acosta S. Decreasing incidence of ruptured abdominal aortic aneurysm already before start of screening. *BMC Cardiovasc Disord* 2016; 16:44.
51. Lilja F, Mani K, Wanhainen A. Editor's Choice - Trend-break in Abdominal Aortic Aneurysm Repair With Decreasing Surgical Workload. *Eur J Vasc Endovasc Surg* 2017; 53(6):811-819.
52. Laine MT, Vanttinen T, Kantonen I, Halmesmaki K, Weselius EM, Laukontaus S, Salenius J, Aho PS, Venermo M. Rupture of Abdominal Aortic Aneurysms in Patients Under Screening Age and Elective Repair Threshold. *Eur J Vasc Endovasc Surg* 2016; 51(4):511-6.
53. Wanhainen A, Mani K, Björck M. The value of a nationwide vascular registry in understanding contemporary time trends of abdominal aortic aneurysm repair. *Scand J Surg* 2008; 97(2):142-5.
54. Laine MT, Laukontaus SJ, Kantonen I, Venermo M. Population-based study of ruptured abdominal aortic aneurysm. *Br J Surg* 2016; 103(12):1634-1639.
55. Karthikesalingam A, Holt PJ, Vidal-Diez A, Ozdemir BA, Poloniecki JD, Hinchliffe RJ, Thompson MM. Mortality from ruptured abdominal aortic aneurysms: clinical lessons from a comparison of outcomes in England and the USA. *Lancet* 2014; 383(9921):963-9.
56. Gunnarsson K, Wanhainen A, Djavani Gidlund K, Björck M, Mani K. Endovascular Versus Open Repair as Primary Strategy for Ruptured Abdominal Aortic Aneurysm: A National Population-based Study. *Eur J Vasc Endovasc Surg* 2016; 51(1):22-8.
57. Karthikesalingam A, Wanhainen A, Holt PJ, Vidal-Diez A, Brownrigg JR, Shpitser I, Björck M, Thompson MM, Mani K. Comparison of long-term mortality after ruptured abdominal aortic aneurysm in England and Sweden. *Br J Surg* 2016; 103(3):199-206.
58. Choke E, Vijaynagar B, Thompson J, Nasim A, Bown MJ, Sayers RD. Changing epidemiology of abdominal aortic aneurysms in England and Wales: older and more benign? *Circulation* 2012; 125(13):1617-25.
59. Sidloff D, Stather P, Dattani N, Bown M, Thompson J, Sayers R, Choke E. Aneurysm global epidemiology study: public health measures can further reduce abdominal aortic aneurysm mortality. *Circulation* 2014; 129(7):747-53.
60. Sampson UK, Norman PE, Fowkes FG, Aboyans V, Song Y, Harrell FE, Jr., Forouzanfar MH, Naghavi M, Denenberg JO, McDermott MM, Criqui MH, Mensah GA, Ezzati M, Murray C. Estimation of global and regional incidence and prevalence of abdominal aortic aneurysms 1990 to 2010. *Glob Heart* 2014; 9(1):159-70.

61. von Allmen RS, Anjum A, Powell JT. Incidence of descending aortic pathology and evaluation of the impact of thoracic endovascular aortic repair: a population-based study in England and Wales from 1999 to 2010. *Eur J Vasc Endovasc Surg* 2013; 45(2):154-9.
62. Geisbusch S, Kuehnl A, Salvermoser M, Reutersberg B, Trenner M, Eckstein HH. Increasing Incidence of Thoracic Aortic Aneurysm Repair in Germany in the Endovascular Era: Secondary Data Analysis of the Nationwide German DRG Microdata. *Eur J Vasc Endovasc Surg* 2019; 57(4):499-509.
63. Olsson C, Thelin S, Ståhle E, Ekbom A, Granath F. Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002. *Circulation* 2006; 114(24):2611-8.
64. Hammo S, Larzon T, Hultgren R, Wanhainen A, Mani K, Resch T, Falkenberg M, Forssell C, Sonesson B, Pirouzram A, Roos H, Hellgren T, Khan S, Hoijer J, Wahlgren CM. Outcome After Endovascular Repair of Ruptured Descending Thoracic Aortic Aneurysm: A National Multicentre Study. *Eur J Vasc Endovasc Surg* 2019; 57(6):788-794.
65. Schlosser FJ, Tangelder MJ, Verhagen HJ, van der Heijden GJ, Muhs BE, van der Graaf Y, Moll FL. Growth predictors and prognosis of small abdominal aortic aneurysms. *J Vasc Surg* 2008; 47(6):1127-33.
66. Thompson AR, Cooper JA, Ashton HA, Hafez H. Growth rates of small abdominal aortic aneurysms correlate with clinical events. *Br J Surg* 2010; 97(1):37-44.
67. Brady AR, Thompson SG, Fowkes FG, Greenhalgh RM, Powell JT. Abdominal aortic aneurysm expansion: risk factors and time intervals for surveillance. *Circulation* 2004; 110(1):16-21.
68. Thanigaimani S, Singh TP, Unosson J, Phie J, Moxon J, Wanhainen A, Golledge J. Association Between Metformin Prescription and Abdominal Aortic Aneurysm Growth and Clinical Events: a Systematic Review and Meta-Analysis. *Eur J Vasc Endovasc Surg* 2021.
69. Golledge J, Morris DR, Pinchbeck J, Rowbotham S, Jenkins J, Bourke M, Bourke B, Norman PE, Jones R, Moxon JV. Metformin Prescription is Associated with a Reduction in the Combined Incidence of Surgical Repair and Rupture Related Mortality in Patients with Abdominal Aortic Aneurysm. *Eur J Vasc Endovasc Surg* 2018.
70. Unosson J, Wågsäter D, Bjarnegård N, De Basso R, Welander M, Mani K, Gottsäter A, Wanhainen A. Metformin Prescription Associated with Reduced Abdominal Aortic Aneurysm Growth Rate and Reduced Chemokine Expression in a Swedish Cohort. *Ann Vasc Surg* 2021; 70:425-433.
71. Wanhainen A, Unosson J, Mani K, Gottsäter A, Investigators MT. The Metformin for Abdominal Aortic Aneurysm Growth Inhibition (MAAAGI) Trial. *Eur J Vasc Endovasc Surg* 2021; 61(4):710-711.
72. Budtz-Lilly J, Björck M, Venermo M, Debus S, Behrendt CA, Altreuther M, Beiles B, Szeberin Z, Eldrup N, Danielsson G, Thomson I, Wigger P, Khashram M, Loftus I, Mani K. The Impact of Centralisation and Endovascular Aneurysm Repair on Treatment of Ruptured Abdominal Aortic Aneurysms Based on International Registries. *Eur J Vasc Endovasc Surg* 2018.

73. The UK Small Aneurysm Trial Participants. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. The UK Small Aneurysm Trial Participants. *Lancet* 1998; 352(9141):1649-55.
74. Powell JT, Gotensparre SM, Sweeting MJ, Brown LC, Fowkes FG, Thompson SG. Rupture rates of small abdominal aortic aneurysms: a systematic review of the literature. *Eur J Vasc Endovasc Surg* 2011; 41(1):2-10.
75. Parkinson F, Ferguson S, Lewis P, Williams IM, Twine CP, South East Wales Vascular N. Rupture rates of untreated large abdominal aortic aneurysms in patients unfit for elective repair. *J Vasc Surg* 2015; 61(6):1606-12.
76. Lederle FA, Johnson GR, Wilson SE, Ballard DJ, Jordan WD, Jr., Blebea J, Littooy FN, Freischlag JA, Bandyk D, Rapp JH, Salam AA. Rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair. *Jama* 2002; 287(22):2968-72.
77. Davies RR, Goldstein LJ, Coady MA, Tittle SL, Rizzo JA, Kopf GS, Elefteriades JA. Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. *Ann Thorac Surg* 2002; 73(1):17-27; discussion 27-8.
78. Coady MA, Rizzo JA, Hammond GL, Kopf GS, Elefteriades JA. Surgical intervention criteria for thoracic aortic aneurysms: a study of growth rates and complications. *Ann Thorac Surg* 1999; 67(6):1922-6; discussion 1953-8.
79. Conrad MF, Cambria RP. Contemporary management of descending thoracic and thoracoabdominal aortic aneurysms: endovascular versus open. *Circulation* 2008; 117(6):841-52.
80. Dapunt OE, Galla JD, Sadeghi AM, Lansman SL, Mezrow CK, de Asla RA, Quintana C, Wallenstein S, Ergin AM, Griepp RB. The natural history of thoracic aortic aneurysms. *J Thorac Cardiovasc Surg* 1994; 107(5):1323-32; discussion 1332-3.
81. Boczar KE, Cheung K, Boodhwani M, Beauchesne L, Dennie C, Nagpal S, Chan K, Coutinho T. Sex Differences in Thoracic Aortic Aneurysm Growth. *Hypertension* 2019; 73(1):190-196.
82. Riambau V, Bockler D, Brunkwall J, Cao P, Chiesa R, Coppi G, Czerny M, Fraedrich G, Haulon S, Jacobs MJ, Lachat ML, Moll FL, Setacci C, Taylor PR, Thompson M, Trimarchi S, Verhagen HJ, Verhoeven EL, Esvs Guidelines C, Kolh P, de Borst GJ, Chakfe N, Debus ES, Hinchliffe RJ, Kakkos S, Koncar I, Lindholt JS, Vega de Ceniga M, Vermassen F, Verzini F, Document R, Kolh P, Black JH, 3rd, Busund R, Bjorck M, Dake M, Dick F, Eggebrecht H, Evangelista A, Grabenwoger M, Milner R, Naylor AR, Ricco JB, Rousseau H, Schmidli J. Editor's Choice - Management of Descending Thoracic Aorta Diseases: Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2017; 53(1):4-52.
83. Chau KH, Elefteriades JA. Natural history of thoracic aortic aneurysms: size matters, plus moving beyond size. *Prog Cardiovasc Dis* 2013; 56(1):74-80.
84. Coady MA, Rizzo JA, Hammond GL, Mandapati D, Darr U, Kopf GS, Elefteriades JA. What is the appropriate size criterion for resection of thoracic aortic aneurysms? *J Thorac Cardiovasc Surg* 1997; 113(3):476-91; discussion 489-91.

85. (SCDR) TSCoDR. Cause of death 2018. Available at: http://www.socialstyrelsen.se/statistics/statisticaldatabase/help/causeofdeath.
86. Reimerink JJ, van der Laan MJ, Koelemay MJ, Balm R, Legemate DA. Systematic review and meta-analysis of population-based mortality from ruptured abdominal aortic aneurysm. *Br J Surg* 2013; 100(11):1405-13.
87. Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, Dick F, van Herwaarden J, Karkos C, Koelemay M, Kolbel T, Loftus I, Mani K, Melissano G, Powell J, Szeberin Z, Esvs Guidelines C, de Borst GJ, Chakfe N, Debus S, Hinchliffe R, Kakkos S, Koncar I, Kolh P, Lindholt JS, de Vega M, Vermassen F, Document R, Björck M, Cheng S, Dalman R, Davidovic L, Donas K, Earnshaw J, Eckstein HH, Golledge J, Haulon S, Mastracci T, Naylor R, Ricco JB, Verhagen H. Editor's Choice - European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms. *Eur J Vasc Endovasc Surg* 2019; 57(1):8-93.
88. Ultee KHJ, Zettervall SL, Soden PA, Buck DB, Deery SE, Shean KE, Verhagen HJM, Schermerhorn ML. The impact of endovascular repair on management and outcome of ruptured thoracic aortic aneurysms. *J Vasc Surg* 2017; 66(2):343-352 e1.
89. Budtz-Lilly J, Björck M, Venermo M, Debus S, Behrendt CA, Altreuther M, Beiles B, Szeberin Z, Eldrup N, Danielsson G, Thomson I, Wigger P, Khashram M, Loftus I, Mani K. Editor's Choice - The Impact of Centralisation and Endovascular Aneurysm Repair on Treatment of Ruptured Abdominal Aortic Aneurysms Based on International Registries. *Eur J Vasc Endovasc Surg* 2018; 56(2):181-188.
90. Jonker FH, Verhagen HJ, Lin PH, Heijmen RH, Trimarchi S, Lee WA, Moll FL, Atamneh H, Rampoldi V, Muhs BE. Open surgery versus endovascular repair of ruptured thoracic aortic aneurysms. *J Vasc Surg* 2011; 53(5):1210-6.
91. Swedvasc. Årsrapport 2020. 2021.
92. Conrad MF, Ergul EA, Patel VI, Paruchuri V, Kwolek CJ, Cambria RP. Management of diseases of the descending thoracic aorta in the endovascular era: a Medicare population study. *Ann Surg* 2010; 252(4):603-10.
93. Baderkhan H, Haller O, Wanhainen A, Björck M, Mani K. Follow-up after endovascular aortic aneurysm repair can be stratified based on first postoperative imaging. *Br J Surg* 2018; 105(6):709-718.
94. Upchurch GR, Jr., Escobar GA, Azizzadeh A, Beck AW, Conrad MF, Matsumura JS, Murad MH, Perry RJ, Singh MJ, Veeraswamy RK, Wang GJ. Society for Vascular Surgery clinical practice guidelines of thoracic endovascular aortic repair for descending thoracic aortic aneurysms. *J Vasc Surg* 2021; 73(1S):55S-83S.
95. Bown MJ, Sutton AJ, Bell PR, Sayers RD. A meta-analysis of 50 years of ruptured abdominal aortic aneurysm repair. *Br J Surg* 2002; 89(6):714-30.
96. IMPROVE. Powell JT, Sweeting MJ, Thompson MM, Ashleigh R, Bell R, Gomes M, Greenhalgh RM, Grieve R, Heatley F, Hinchliffe RJ, Thompson SG, Ulug P. Endovascular or open repair strategy for ruptured abdominal aortic aneurysm: 30 day outcomes from IMPROVE randomised trial. *BMJ* 2014; 348:f7661.

97. Reimerink JJ, Hoornweg LL, Vahl AC, Wisselink W, van den Broek TA, Legemate DA, Reekers JA, Balm R, Amsterdam Acute Aneurysm Trial C. Endovascular repair versus open repair of ruptured abdominal aortic aneurysms: a multicenter randomized controlled trial. *Ann Surg* 2013; 258(2):248-56.
98. Veith FJ, Lachat M, Mayer D, Malina M, Holst J, Mehta M, Verhoeven EL, Larzon T, Gennai S, Coppi G, Lipsitz EC, Gargiulo NJ, van der Vliet JA, Blankensteijn J, Buth J, Lee WA, Biasi G, Deleo G, Kasirajan K, Moore R, Soong CV, Cayne NS, Farber MA, Raithel D, Greenberg RK, van Sambeek MR, Brunkwall JS, Rockman CB, Hinchliffe RJ. Collected world and single center experience with endovascular treatment of ruptured abdominal aortic aneurysms. *Ann Surg* 2009; 250(5):818-24.
99. Badger S, Forster R, Blair PH, Ellis P, Kee F, Harkin DW. Endovascular treatment for ruptured abdominal aortic aneurysm. *Cochrane Database Syst Rev* 2017; 5:CD005261.
100. IMPROVE. Comparative clinical effectiveness and cost effectiveness of endovascular strategy v open repair for ruptured abdominal aortic aneurysm: three year results of the IMPROVE randomised trial. *BMJ* 2017; 359:j4859.
101. Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, Dick F, van Herwaarden J, Karkos C, Koelemay M, Kolbel T, Loftus I, Mani K, Melissano G, Powell J, Szeberin Z, Esvs Guidelines C, de Borst GJ, Chakfe N, Debus S, Hinchliffe R, Kakkos S, Koncar I, Kolh P, Lindholdt J, de Vega M, Vermassen F, Document R, Björck M, Cheng S, Dalman R, Davidovic L, Donas K, Earnshaw J, Eckstein HH, Golledge J, Haulon S, Mastracci T, Naylor R, Ricco JB, Verhagen H. European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms. *Eur J Vasc Endovasc Surg* 2018.
102. IMPROVE. Endovascular strategy or open repair for ruptured abdominal aortic aneurysm: one-year outcomes from the IMPROVE randomized trial. *Eur Heart J* 2015; 36(31):2061-2069.
103. Desgranges P, Kobeiter H, Katsahian S, Bouffi M, Gouny P, Favre JP, Alsac JM, Sobocinski J, Julia P, Alimi Y, Steinmetz E, Haulon S, Alric P, Canaud L, Castier Y, Jean-Baptiste E, Hassen-Khodja R, Lermusiaux P, Feugier P, Destrieux-Garnier L, Charles-Nelson A, Marzelle J, Majewski M, Bourmaud A, Becquemin JP, Investigators E. Editor's Choice - ECAR (Endovasculaire ou Chirurgie dans les Anevrysmes aorto-iliaques Rompus): A French Randomized Controlled Trial of Endovascular Versus Open Surgical Repair of Ruptured Aorto-iliac Aneurysms. *Eur J Vasc Endovasc Surg* 2015; 50(3):303-10.
104. Hinchliffe RJ, Bruijstens L, MacSweeney ST, Braithwaite BD. A randomised trial of endovascular and open surgery for ruptured abdominal aortic aneurysm - results of a pilot study and lessons learned for future studies. *Eur J Vasc Endovasc Surg* 2006; 32(5):506-13; discussion 514-5.
105. Ersryd S, Djavani-Gidlund K, Wanhainen A, Björck M. Editor's Choice - Abdominal Compartment Syndrome After Surgery for Abdominal Aortic Aneurysm: A Nationwide Population Based Study. *Eur J Vasc Endovasc Surg* 2016; 52(2):158-65.

106. Ersryd S, Djavani Gidlund K, Wanhainen A, Smith L, Björck M. Editor's Choice - Abdominal Compartment Syndrome after Surgery for Abdominal Aortic Aneurysm: Subgroups, Risk Factors, and Outcome. *Eur J Vasc Endovasc Surg* 2019; 58(5):671-679.
107. Champagne BJ, Lee EC, Valerian B, Mulhotra N, Mehta M. Incidence of colonic ischemia after repair of ruptured abdominal aortic aneurysm with endograft. *J Am Coll Surg* 2007; 204(4):597-602.
108. Ultee KH, Zettervall SL, Soden PA, Darling J, Bertges DJ, Verhagen HJ, Schermerhorn ML, Vascular Study Group of New E. Incidence of and risk factors for bowel ischemia after abdominal aortic aneurysm repair. *J Vasc Surg* 2016; 64(5):1384-1391.
109. Barbato JE, Kim JY, Zenati M, Abu-Hamad G, Rhee RY, Makaroun MS, Cho JS. Contemporary results of open repair of ruptured descending thoracic and thoracoabdominal aortic aneurysms. *J Vasc Surg* 2007; 45(4):667-76.
110. Jonker FH, Trimarchi S, Verhagen HJ, Moll FL, Sumpio BE, Muhs BE. Meta-analysis of open versus endovascular repair for ruptured descending thoracic aortic aneurysm. *J Vasc Surg* 2010; 51(4):1026-32, 1032 e1-1032 e2.
111. Alsawas M, Zaiem F, Larrea-Mantilla L, Almasri J, Erwin PJ, Upchurch GR, Jr., Murad MH. Effectiveness of surgical interventions for thoracic aortic aneurysms: A systematic review and meta-analysis. *J Vasc Surg* 2017; 66(4):1258-1268 e8.
112. Lopez Espada C, Linares Palomino JP, Dominguez Gonzalez JM, Iborra Ortega E, Lozano Vilardell P, Solanich Valldaura T, Volo Perez G, Blanco Canibano E, Alvarez Salgado A, Fernandez Fernandez JC, Hernando Rydings M, Miralles Hernandez M. Endovascular Treatment of Descending Thoracic Aortic Pathology: Results of the Regis-TEVAR Study. *Ann Vasc Surg* 2020; 67:306-315.
113. Elbadawi A, Elgendy IY, Jimenez E, Omer MA, Shahin HI, Ogunbayo GO, Paniagua D, Jneid H. Trends and Outcomes of Elective Thoracic Aortic Repair and Acute Thoracic Aortic Syndromes in the United States. *Am J Med* 2021; 134(7):902-909 e5.
114. Ogawa Y, Watkins AC, Lingala B, Nathan I, Chiu P, Iwakoshi S, He H, Lee JT, Fischbein M, Woo YJ, Dake MD. Improved midterm outcomes after endovascular repair of nontraumatic descending thoracic aortic rupture compared with open surgery. *J Thorac Cardiovasc Surg* 2021; 161(6):2004-2012.
115. Schermerhorn ML, Giles KA, Hamdan AD, Dalhberg SE, Hagberg R, Pomposelli F. Population-based outcomes of open descending thoracic aortic aneurysm repair. *J Vasc Surg* 2008; 48(4):821-7.
116. Abraha I, Romagnoli C, Montedori A, Cirocchi R. Thoracic stent graft versus surgery for thoracic aneurysm. *Cochrane Database Syst Rev* 2016(6):CD006796.
117. Sir Thomas Percival (1740-1804):Medical ethics; or, a code of institutes adapted to the professional conduct of physicians and surgeons, in hospital praxis in relation to apothecaries and in cases which may require a knowledge of law. *Br Foreign Med Chir Rev* 1850.
118. Kaska SC, Weinstein JN. Historical perspective. Ernest Amory Codman, 1869-1940. A pioneer of evidence-based medicine: the end result idea. *Spine (Phila Pa 1976)* 1998; 23(5):629-33.

119. McLendon WW. Ernest A. Codman, MD (1869-1940), the end result idea, and The Product of a Hospital. The challenge of a man ahead of his time and perhaps ours. *Arch Pathol Lab Med* 1990; 114(11):1101-4.
120. Greer RB, 3rd. Codman's end-result idea. *Orthop Rev* 1993; 22(8):897-8.
121. Lönnroth L. Kyrkoarkivet, från medeltiden till idag. *Riksarkivets årsbok* 2016:45-64.
122. (SCB) CBoS. SCB:s historia. *https://www.scb.se/om-scb/scbs-verksamhet/scbs-historia/* 2021.
123. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009; 24(11):659-67.
124. Emilsson L, Lindahl B, Koster M, Lambe M, Ludvigsson JF. Review of 103 Swedish Healthcare Quality Registries. *J Intern Med* 2015; 277(1):94-136.
125. Jacobsson-Ekman G LB, Nordin A. National quality registries in Swedish health care. *Karolinska Institutet University Press* 2016.
126. kvalitetsregister N. Valideringshandbok. *https://skr.se/kvalitetsregister/drivaregister/valideringshandbok.54585.html* 2021.
127. Bergqvist D, Troëng T, Einarsson E, Elfström J, Norgren L. Vascular surgical audit during a 5-year period. Steering committee on behalf of the Swedish Vascular Registry (Swedvasc). *Eur J Vasc Surg* 1994; 8(4):472-7.
128. Thomas Troëng AL. Kvalitetsregistret Swedvasc sporrar KärlKirurgin. *Läkartidningen* 2011; 08/2011.
129. Troeng T, Malmstedt J, Björck M. External Validation of the Swedvasc Registry: A First-time Individual Cross-matching with the Unique Personal Identity Number. *Eur J Vasc Endovasc Surg* 2008; 36(6):705-12.
130. Venermo M, Lees T. International Vascunet Validation of the Swedvasc Registry. *Eur J Vasc Endovasc Surg* 2015; 50(6):802-8.
131. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011; 11:450.
132. welfare NNboha. Quality of data on The National Patient Registry. *https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/patientregistret/bortfall-och-kvalitet/* 2021.
133. (NBHW) Nbohaw. Quality on data on the Cause of Death Registry. *https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/dodsorsaksregistret/bortfall-och-kvalitet/* 2021.
134. Svensjö S, Björck M, Gurtelschmid M, Djavani Gidlund K, Hellberg A, Wanhainen A. Low prevalence of abdominal aortic aneurysm among 65-year-old Swedish men indicates a change in the epidemiology of the disease. *Circulation* 2011; 124(10):1118-23.
135. Mani K, Björck M, Wanhainen A. Changes in the management of infrarenal abdominal aortic aneurysm disease in Sweden. *Br J Surg* 2013; 100(5):638-44.
136. Central Bureau of Statistics (SCB) S. Living Conditions Surveys (ULF/SILC), Tobacco habits 1980-2016 2018. Available at: http://www.scb.se/hitta-statistik/statistik-efter-amne/levnadsforhallanden/levnadsforhallanden/undersokningarna-av-levnadsforhallanden-ulf-silc/pong/tabell-och-diagram/halsa/halsa--fler-indikatorer/.

137. Mani K, Lees T, Beiles B, Jensen LP, Venermo M, Simo G, Palombo D, Halbakken E, Troëng T, Wigger P, Björck M. Treatment of abdominal aortic aneurysm in nine countries 2005-2009: a vascunet report. *Eur J Vasc Endovasc Surg* 2011; 42(5):598-607.
138. van Beek SC, Conijn AP, Koelemay MJ, Balm R. Editor's Choice - Endovascular aneurysm repair versus open repair for patients with a ruptured abdominal aortic aneurysm: a systematic review and meta-analysis of short-term survival. *Eur J Vasc Endovasc Surg* 2014; 47(6):593-602.
139. Kontopodis N, Galanakis N, Antoniou SA, Tsetis D, Ioannou CV, Veith FJ, Powell JT, Antoniou GA. Meta-Analysis and Meta-Regression Analysis of Outcomes of Endovascular and Open Repair for Ruptured Abdominal Aortic Aneurysm. *Eur J Vasc Endovasc Surg* 2020; 59(3):399-410.
140. Mani K, Björck M, Lundkvist J, Wanhainen A. Improved long-term survival after abdominal aortic aneurysm repair. *Circulation* 2009; 120(3):201-11.
141. D'Oria M, Hanson KT, Shermerhorn M, Bower TC, Mendes BC, Shuja F, Oderich GS, DeMartino RR. Editor's Choice - Short Term and Long Term Outcomes After Endovascular or Open Repair for Ruptured Infrarenal Abdominal Aortic Aneurysms in the Vascular Quality Initiative. *Eur J Vasc Endovasc Surg* 2020; 59(5):703-716.
142. Society TSC. Cancer statistics. 2021.
143. Drudi LM, Ades M, Landry T, Gill HL, Grenon SM, Steinmetz OK, Afilalo J. Scoping review of frailty in vascular surgery. *J Vasc Surg* 2019; 69(6):1989-1998 e2.
144. von Allmen RS, Anjum A, Powell JT. Outcomes after endovascular or open repair for degenerative descending thoracic aortic aneurysm using linked hospital data. *Br J Surg* 2014; 101(10):1244-51.
145. Hellgren T, Beck AW, Behrendt CA, Becker D, Beiles B, Boyle JR, Jormalainen M, Koncar I, Espada CL, Setacci C, Settembre N, Sutzko DC, Szeberin Z, Thomson I, Venermo M, Mani K. Thoracic endovascular aortic repair practice in 13 countries: A report from VASCUNET and the International Consortium of Vascular Registries. *Ann Surg* 2020.
146. Harky A, Kai Chan JS, Ming Wong CH, Bashir M. Open versus Endovascular Repair of Descending Thoracic Aortic Aneurysm Disease: A Systematic Review and Meta-analysis. *Ann Vasc Surg* 2019; 54:304-315 e5.
147. Hellgren T, Wanhainen A, Steuer J, Mani K. Outcome of endovascular repair for intact and ruptured thoracic aortic aneurysms. *J Vasc Surg* 2017; 66(1):21-28.
148. Goodney PP, Travis L, Lucas FL, Fillinger MF, Goodman DC, Cronenwett JL, Stone DH. Survival after open versus endovascular thoracic aortic aneurysm repair in an observational study of the Medicare population. *Circulation* 2011; 124(24):2661-9.
149. Rich N, Tucker LY, Okuhn S, Hua H, Hill B, Goodney P, Chang R. Long-term freedom from aneurysm-related mortality remains favorable after endovascular abdominal aortic aneurysm repair in a 15-year multicenter registry. *J Vasc Surg* 2019.
150. Oliveira-Pinto J, Soares-Ferreira R, Oliveira NFG, Bastos Goncalves FM, Hoeks S, Van Rijn MJ, Raa ST, Mansilha A, Verhagen HJM. Comparison of midterm results of endovascular aneurysm repair for ruptured and elective abdominal aortic aneurysms. *J Vasc Surg* 2019.

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