Aspects of endovascular treatment of abdominal aortic aneurysms
He could say to me: "Percy, why does a streetcar have to weigh ten times more than a bus? Why do train coaches have to be built so that the passengers have to climb up a whole meter just to come in?"

He could ask a hundred such questions and then he would sketch out new solutions. Even if only a small percent of his ideas could be realized and put into practice, the dividends would be fantastic.

Percy Barnevik, former CEO of ABB, about his boss and mentor Curt Nicolin, from his autobiography “Jag vill förändra världen” (2011).
Aspects of endovascular treatment of abdominal aortic aneurysms
Abstract


Despite considerable improvements in perioperative care, anesthesiology and intensive care, operative mortality after open repair (OR) for ruptured abdominal aortic aneurysm (RAAA) is still reported as high as 40-50% with just a slight decrease since the 50th. Endovascular aortic repair (EVAR) of a RAAA was first performed successfully in 1994 and the first case series in 2000 reported just 10% mortality.

In the first study we made a retrospective review of EVAR and OR in 41 patients with RAAA and found a trend for lower mortality after EVAR, 13% (2 of 15) compared to 46% (12 of 26) in the OR group.

In the second study we retrospectively analysed the complication rate for access closure with the fascia suture technique (FST) of 131 femoral arteries. The acute failure rate was 12% and half of failures appeared perioperatively and the rest postoperatively, requiring reoperations within 24 hours. Ankle-brachial index did not change from pre- to postoperatively.

In the third study we performed a prospective, randomized, two-centre trial of 100 patients undergoing endovascular repair of aortic aneurysms and dissections where access closure with FST was compared with a suture-mediated closure device (Prostar). We found that access closure time was faster and cost was lower for FST than for Prostar. The latter required a 54% longer procedure time and the median difference of cost was 800€. Complication rate was not significantly different. An independent risk factor was operator experience.

The forth study was a retrospective review of 473 consecutive patients with RAAA recruited 1998-2011 at two centers to assess how a preferential EVAR strategy could improve outcome and it showed that it was possible to replace open repair with EVAR and keeping a low 30-day mortality (24%) and few patients (4%) where advised to medical treatment only.

From this thesis it can be concluded that knowledge and technology exist today to replace OR and that cost can be reduced.

Keywords: abdominal aortic aneurysm, rupture, endovascular aneurysm repair, open repair, percutaneous closure, fascia suture, cribriform fascia, randomized controlled trial, cost analysis, outcome analysis, mortality.

Thomas Larzon, School of Health and Medical Sciences
Örebro University, SE-701 82 Örebro, Sweden, thomas.larzon@orebroll.se
List of papers

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


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## Abbreviations

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<td>AAA</td>
<td>Abdominal aortic aneurysm</td>
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<td>ABI</td>
<td>Ankle-brachial index</td>
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<td>ACS</td>
<td>Abdominal compartment syndrome</td>
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<td>CFA</td>
<td>Common femoral artery</td>
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<td>CIA</td>
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<td>CT</td>
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<td>F</td>
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<td>PTFE</td>
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<td>RAAA</td>
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Introduction

Pathology
The natural course of the abdominal aorta is a dilatation with increasing age (Steinberg 1965, Pedersen 1993). There is a significant correlation between size and body surface area and the diameter is significantly larger in men than in women from about 25 years of age (Sonesson 1994).

The aortic wall consists mainly of elastin and collagen arranged in elastic lamellae. With increasing age the elastin component decreases and as the protecting effect of elastin is lost the blood pressure load will affect the collagen. The altered matrix composition leads to a decreased compliance of the aortic wall and the aorta will dilate in some patients (Sonesson 1993).

Today, most aneurysms have an atherosclerotic etiology while the incidence of infectious or mycotic aneurysms has declined markedly. Heredity plays an important role with an increased incidence for siblings (Norrgård 1984, Bengtsson 1989). Congenital diseases with connective tissue defects, such as Ehlers-Danlos syndrome (De Paepe 2012) and Marfan’s syndrome predispose for aneurysm formation (Hollister 1990).

Definition
Several definitions are used for an abdominal aortic aneurysm (AAA) (Moher 1992). An infrarenal aortic diameter of $\geq$30 mm has been considered an aneurysm (Steinberg 1965, Leopold 1970, McGregor 1976), while the most accepted definition today is an infrarenal aortic diameter 1.5 times larger than the expected and relates to the Ad Hoc Committee of the joint councils of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery (Johnston 1991). This definition takes in account individual variations.

Prevalence and natural history
The knowledge about AAA prevalence is based on autopsy studies and screening programs. In a study from Malmö, Sweden, an autopsy rate of 85% was achieved. The overall prevalence of AAA in this cohort was found to be 4.3% for men and 2.1% for women and was age related (Bengtsson 1992). In a screening program of more than 125,000 veterans in the United States between the age of 50 and 79 years, AAA $\geq$3 cm was detected in 3.6% of the subjects and $\geq$4 cm in 1.2% (Lederle 2000).

AAA are usually asymptomatic but expand gradually and may eventually rupture. The risk of rupture is associated with the size of the aneurysm.
The growth rate varies among individuals but the expected expansion rate is 2-5 mm per year for small aneurysms (Cronenwett 1990, Delin 1985, Schlösser 2008). Aneurysms less than 50 mm in diameter rarely rupture (Scott 1998) but it is estimated that around 50% of patients with an AAA larger than 7 cm in diameter will die from their rupture if it is not resected (Darling 1977).

**Risk factors**

Smoking is the most important risk factor for AAA with an odds ratio of 5.07. Other risk factors are family history (odds ratio 1.94) and atherosclerotic diseases (odds ratio 1.66), while female sex and diabetes are negatively associated with AAA (Lederle 1997, Lederle 2000). Hypertension and hypercholesterolemia are also risk factors for occlusive vascular disease and a theory is that AAA is just a different manifestation of aortic atherosclerosis than occlusive disease (Pleumeekers 1995, Singh 2001, Törnwall 2001, Zarins 2001). This theory is however challenged by studies suggesting that chronic inflammation and degradation of elastin in AAA possibly are immune-mediated. The inflammation may be induced by the chemotactic substances of elastin-derived peptides (Patel 1995, Satta 1998).

Deaths from a ruptured AAA have decreased by a third from 1997, almost twofold in men, as reported from England and Wales. During the same period the prevalence of smoking has fallen from 18 to 13 percent (similar in men and women) in the general population aged 65 years and older (Anjum 2012). Almost half of the reduction in mortality from ruptured aneurysms for those above 65 years of age can be explained by a change of smoking habits, while also an increased rate of elective surgery may contribute. Likewise, the prescription of lipid-lowering drugs has increased ten-fold (British Heart Foundation 2011) and may be an associated factor. A similar trend is reported from the USA (Lederle 2011).

A lower-than-expected prevalence of AAA among 65-year-old men was found in a Swedish screening program. A change in smoking habits may be one reason (Svensjö 2011). Thirteen percent of the entire population reported to be current smokers, one third of figures achieved from the 1980s.

**Gender**

Ultrasonographic investigations have demonstrated a sex-related difference in diameter and compliance of the normal human abdominal aorta, indicating that degenerative changes appear later in females (Länne 1992, Sonesson 1993). In the UK Small Aneurysm Trial it was found that the risk
for rupture was four times higher among women than among men with aneurysms in the range of 40 - 55 mm (The UK Small Aneurysm Trial Participants 1998). The mean diameter preceding rupture was smaller in women (5.0 ±0.8 cm) than men (6.0 ±1.4 cm) (p=0.001) (Brown 1999).

Gender differences in treatment and outcome after admission with ruptured abdominal aortic aneurysm (RAAA) have been noticed in the United Kingdom. Women with a ruptured aneurysm were less likely to be treated surgically than men, and their overall mortality rate was higher. Lower rates of surgery in women than in men may contribute to the higher mortality in women, but other explanations are possible (Filipovic 2007). Significantly increased mortality for women was also found in a study from Norway where data from 15 years was gathered. Women were significantly older and had more often autoimmune disease than men (Berge 2012).

Biomarkers might be gender specific for AAA. From a sex perspective plasma concentration of matrix metalloproteinase (MMP)-9 was significantly higher for women than men with equally large AAA and estradiol levels in women with AAA were lower compared to men. The possible protective effect of endogenous estrogen can probably not be explained by a difference in circulating levels of estradiol. (Villard 2012).

**Diagnosis**

Non-ruptured aneurysms are usually diagnosed accidentally during investigations for other purposes. The accuracy of abdominal examination should not be ignored (Venkatasubramaniam 2004) even though it has low sensitivity especially in obese patients (Lederle 1988, Karkos 2000). With the introduction of modern non-invasive techniques such as ultrasound and computed tomography (CT) it has been possible to investigate populations for the presence of AAA with great accuracy. Both techniques have proved to be reliable. Closer correlation to the aneurysmal diameter measured at surgery is obtained by CT and underestimation of size by ultrasound is a frequent finding (Gomes 1978). Ultrasound is an inexpensive technique, easy and fast to perform, and is normally the method used for screening programs (Wilmink 2002).

The introduction of multidetector CT (MDCT) has improved and expanded the clinical applications for this imaging method. It has not only increased the quality of the images but also made the examination much faster (Rubin 2003). MDCT has become the reference standard in the diagnosis and follow-up of patients undergoing endovascular aortic repair (EVAR) in many centers (Iezzi 2006).

Time-resolved CT has a high diagnostic performance for the detection and classification of different types of endoleaks (Sommer 2012). Time-
resolved magnetic resonance angiography is also highly effective in classifying endoleaks and can demonstrate flow direction (Cohen 2008).

Contrast-enhanced ultrasonography is an alternative to CT in the follow-up of patients after EVAR. Drawbacks with CT are contrast-induced nephropathy, radiation, and costs while ultrasound is harmless and inexpensive but operator dependent (Beales 2011). Thus using ultrasound for surveillance avoids the risk associated with lifelong annual CT, including cumulative radiation dose and nephrotoxic contrast agent load (Clevert 2009, Ten Bosch 2010).

**Indications for surgery**

Large asymptomatic AAA (> 5.5 cm in diameter) are usually operated on while very small AAA (< 4.0 cm diameter) are monitored with ultrasonography. In a review of four randomized trials comparing long-term survival in patients with AAA 4.0 to 5.5 cm in diameter, who received immediate repair versus routine ultrasound surveillance, an early survival benefit was shown in the surveillance group (due to 30-day operative mortality with surgery) but there were no significant differences in long-term survival (Filardo 2012). Elective surgery for aneurysms 4.5-5.5 in diameter should be considered only if they are expanding by more than 1.0 cm in one year or for symptomatic patients (The UK Small Aneurysm Trial Participants 1998). Women may be operated on for aneurysms reaching a diameter of 5 cm as they tend to rupture earlier (Powell 2004).

**History**

**History of open repair**

A variety of different techniques has been used since the beginning of 19th century. Aneurysmorraphy (Matas 1903), packing of the sac with wires (Power 1903), ligature of the aorta (Matas 1925) and external wrapping (Abbot 1949) were tried. A well-known patient with AAA during this period was Albert Einstein (1879–1955) who had his aneurysm wrapped with cellophane in 1948. It was not until the second postwar period development took off. The introduction of antibiotics and heparin together with novel knowledge about principles for blood replacement and the development of synthetic grafts was the platform for successful aneurysm aortic repair. The first aortic reconstruction with a vein graft was performed by Freeman in 1951 (Freeman 1951). The vein graft ruptured after 6 hours and the patient died. The first reconstruction with a homologous aorta was performed three weeks later (Schafer 1952). This patient died from an upper anastomosis bleeding one month after the operation. Within a
month Dubost performed the first successful reconstruction with a homologous aorta (Dubost 1951). Homografts dominated as the aortic substitute, but serious problems occurred as the structure degraded (Szilagyi 1957). Already in 1953 Shumacker and King (Shumacker 1954) used a synthetic graft which then has been dominating. Dacron grafts were introduced into clinical practice in 1957 by DeBakey (DeBakey 1958) and are still the material of choice. Resection of the aneurysm was replaced by an inlay anastomosis technique in order to diminish the risk of bleeding from the caval vein (Creech 1966).

The mortality rate for elective surgery was for quite a long period almost 20% (Crawford 1981) but has gradually decreased as a result of improved perioperative and postoperative care, not least advances in intensive care. Community based studies show a mortality rate of 4 - 8% (Ernst 1993, Kazmers 1998) with single centers reporting figures of less than 2% (Hertzer 2002, Becquemin 2011) even in octogenarians (Ballotta 2008). The results of treatment depend on a combination of patient condition and the technical complexity of the operative procedure as well as the timing of the operation. Major experienced centers also present the best results (Luft 1979, Hertzer 1984, van der Laan 2012).

**History of endovascular repair**

In the mid 80’s Volodos for the first time inserted an aortic endoprosthesis via a transfemoral approach, that was reported 1986 in Russian (Volodos 1986) and later in English (Volodos 1991). Parallel to this initial experience Parodi worked with a tubular stent graft with fixation only at the proximal end (Parodi 1991). These were all home-made devices based on either self- or balloon-expandable stents covered by graft fabric. The first bifurcated stent graft was developed and implanted by Chuter in 1993 (Chuter 1993). The durability of these first generations of stent grafts were, however, doubtful (Guidoin 2000). Type III endoleak, due to fabric failure or component separation, was a common reason for failure but is rare with newer devices. Suture breakage, barb separation and stent breakage occur frequently, yet clinical consequences, such as endoleak or rupture, are rare (Chuter 2003). Commercially developed stent grafts are now available in a wide variety but basically they are constructed in the same manner with a fabric of polyethylene terephthalate (Dacron) or polytetrafluorethylene (PTFE) attached to a self-expandable stent frame.

Aortic tubular stent grafts are no longer in use because of a tendency to get incomplete distal seal (May 1998). There are two main designs of stent grafts for EVAR today. The aorto-uni-iliac stent graft requires a femoro-femoral cross-over bypass and an occluding device in the contra-lateral
common iliac artery (CIA) to avoid retrograde flow into the aneurysm. Bifurcated stent grafts have become the most common device and may also be inserted percutaneously (Traul 2000).

The outcome of EVAR is very much depending on adequate sealing and proximal fixation. The proximal sealing zone, i.e. the distance from the level of the lowest renal artery to the upper end of the aneurysm is the most important limitation for EVAR.

Distal migration of the stent graft was early recognized as a major problem resulting in problems with the proximal seal. As stent grafts are not healing in the aortic wall (McArthur 2001) fixation is depending on the mechanical properties of the stent. Passive fixation is achieved by the radial force itself of a self-expandable stent, but it is associated with a high risk of migration and today stent grafts are normally supported for an active fixation with barbs or hooks which have been shown to considerably add anchoring strength (Malina 1998). Stent grafts are either fixated just below the renal arteries or have their fixation mechanism at the top of bare springs, separated from the fabric. There is yet no consensus of what is optimal and results are divergent whether supra- or infra-renal fixation is best to prevent migration (Kalliafas 2002, Hager 2012).

Second to a difficult aortic neck comes rejection due to inadequate arterial access or presence of extensive iliac artery aneurysms (Moise 2006). With a new generation of low-profile endoprosthesis commercially available, access in not any longer a major issue. The chief anatomic barriers today are the branched vascular segments.

In recent years, increasingly complex stent graft designs with fenestrations and branches have been used to treat juxtarenal and pararenal aneurysms as well as thoracoabdominal aneurysms (Greenberg 2008). Reports from large single-center series have suggested that juxtarenal aneurysms can be effectively excluded by use of fenestrated stent grafts and are associated with low mortality and morbidity and high rate of target vessel patency (O’Neill 2006, Verhoeven 2010, Amiot 2010). Nationwide results from United Kingdom have been published with 4.1% 30-day mortality and satisfactory mid-term results regarding target vessel loss after 3 years (15%) as well as freedom from late secondary intervention (70%) (British Society for Endovascular Therapy and the Global Collaborators on Advanced Stent-Graft Techniques for Aneurysm Repair (GLOBALSTAR) Registry 2012). Long-term results are not yet available for fenestrated stent grafts.

EVAR is still associated with a significant long-term complication rate requiring reinterventions. The most common complication endoleak, occurs in up to 45% of patients (Stolzmann 2008). High-pressure leaks (type
I and type III) require in general a secondary intervention because of relatively high short-time risk of sac rupture. Low-pressure lesions (type II and type V or endotension) require surveillance to detect changes in sac dimension and treatment is necessary only if there is a significant increase of aneurysm size (Cao 2010). Type IV endoleaks are caused by porosity of the graft fabric and seal spontaneously. Type V endoleak or endotension corresponds to continued aneurysm expansion in the absence of a confirmed endoleak but may represent an undiagnosed endoleak (Golzarian 2006). Endotension is more common with PTFE grafts due to ultra-filtration through graft pores (Gawenda 2003) and creates sac hygroma (Risberg 2004).

**Access techniques**

**Surgical cutdown**

EVAR was initially performed by a surgical exposure of common femoral artery (CFA). Vertical or oblique skin incisions are performed bilaterally. The CFA is located in the femoral triangle where it runs through the femoral canal and is covered anteriorly by the femoral fascia (the cribriform fascia).

Under fluoroscopy a guidewire and a small size sheath are introduced via an anterior wall puncture of CFA, typically followed by arteriotomy (transverse, vertical or V-type) and introduction of a large size sheath using a stiff guidewire. To avoid oozing of blood a vessel-loop can be placed round the artery and the sheath and backflow can be controlled with a vascular clamp. In extensive tortuous iliac anatomy a pull-down manoeuvre or digital stretching of the external iliac artery (EIA) can be used by lifting of the inguinal ligament and using blunt dissection to reach the iliac bifurcation (Lönn 2010). The CFA wall may be mechanically damaged after introducer introduction and an endarterectomy with patch plasty is required.

Another option is retroperitoneal dissection above the inguinal ligament to expose the EIA and/or the CIA. The stent graft can be inserted directly or via a vascular prosthesis sutured end to side to the CIA. In most cases the conduit is temporary (Utikal 2006). Access closure is performed with monofilament sutures (running or interrupted).

Although a surgical cutdown is considered a minor surgical procedure it is associated with postprocedural groin complications such as hematoma, thrombosis, dissection, seroma/lymphocele, femoral nerve injury and delayed wound healing due to infection. The CFA will also be more exposed to longitudinal stress after surgical cut down as compared with total percu-
Percutaneous access
The development of smaller sheath sizes has facilitated a less invasive method to achieve vascular access. The choice of an optimal femoral approach depends on the unique anatomy of each patient. The deep femoral artery is located 2.5 - 5 cm distal to the origin of the CFA. The most superficial part of the CFA is to be found at the level where the artery passes in front of the femoral head. A portion of the CFA overlaps the corresponding vein in the antero-posterior plane in 65% of cases. This relationship is important to know in order to prevent from development of an arteriovenous fistula (Baum 1989).

The optimal puncture site of the CFA is situated between the inguinal ligament and the femoral bifurcation. Different landmarks can be used to optimize the puncture site. In a survey of the superficial landmarks used to select the site of retrograde puncture of the femoral artery for angiography, the inguinal skin crease was located distal to the bifurcation of the CFA in 71.9% of limbs. Therefore the use of the inguinal skin crease should be considered an unreliable guide for puncture of the CFA. The maximal femoral pulse corresponded to the CFA in 92.7% of limbs (Grier 1990). Similar results were seen in another study where it also was demonstrated that the mid-femoral head was positioned distal to the femoral bifurcation in only 1 % of cases (Garrett 2005). As a result of that, fluoroscopy can be reliably used to locate the center of the femoral head (Schnyder 2001). A high puncture site increases the risk of retroperitoneal bleeding that may be massive because of loose connective tissue in the retroperitoneal space and such a bleeding cannot easily be detected by clinical examination in its initial phase. Low puncture sites are associated with formation of hematomas, thrombosis, pseudoaneurysms, dissections and arteriovenous fistulae (Sherev 2005, Altin 1989).

The skin puncture should be made 1 – 2 cm caudal to the planned arterial entry. The site of skin entry should vary, according to the amount of subcutaneous fat. After skin penetration of the needle it should be left lying in order to reduce radiation exposure of the hands of the operator. A fluoroscopy should be performed to evaluate the needle position in relation to the landmarks of the femoral head. After successful puncture of the femoral artery, injection of contrast medium through the needle or a small size sheath, 4-5 French size (F), can be performed. Angiography is usually performed in an anterio-posterior or slightly oblique projection. In case the puncture site is inadvertently too high or too low, manual compression can
be performed or the small size sheath can be left in place to be removed at the end of the procedure (Lönn 2010). Use of a micropuncture set is recommended in difficult cases. Ultrasound-guided puncture can also be implemented. The femoral artery bifurcation can normally be identified and in addition, ultrasonography is able to identify arterial wall disorders as atherosclerotic plaques and calcification. This will reduce the risk for access site complications when closure devices are being used (Oğuzkurt 2012).

**Closure techniques**

**Percutaneous suture-mediated closure devices**

Access closure after percutaneous endovascular aneurysm repair (P-EVAR) utilizing a suture-mediated closure device (SMCD) was first described in 1999 by Haas (Haas 1999). A problem with the Prostar XL device (Abbott Laboratories, Redwood City, CA, USA) was the design to accommodate a maximum of 10 F. Howell showed that the “pre-suturing technique” was applicable (Howell 2002). The device is deployed vertically into the vessel-wall before insertion of the stent graft system using a pair of nitinol needles. After completion of the endovascular procedure the sutures from the device are prepared with saline for lubrication and removal of clots. A sliding knot is formed and slid down onto the arterial wall. Normally two devices are used in large bore sheets up to 24 F. Patient selection has been advised with this closure technique as calcification might deflect the device’s needles and scarred groins and obesity may cause technical difficulties in advancing the device’s slipknots.

The Perclose ProGlide (Abbott Laboratories, Redwood City, CA, USA) is a 6 F SMCD which has been used off-label for the CFA access sites. As with the Prostar device it is deployed vertically into the vessel-wall before insertion of the stent graft system using a pair of nitinol needles. Ending the procedure a pre-tied slip-knot is slid down to the vessel in order to close the access site. At the discretion of the operator, one to three of the ProGlide devices can be used in sheets up to 24 F. An immediate technical success rate of 94-97% has been reported with a late complication rate less than 2 percent (Lee 2008).

In a systematic review the overall success rate of percutaneous arterial closure devices has been reported to be 92% (95% CI, 90.1–93.9) with an access complication rate of 4.4% (95% CI, 3.5–5.3) and P-EVAR was associated with fewer access related complications than after surgical cut-down (RR 0.47, 95%, CI 0.28-0.71, p=0.004) (Malkawi 2010). SMCD has not been seen as an alternative for emergency procedures as it requires
the pre-suturing technique and another drawback is the additional increase in cost.

The endovascular suture technique has been compared with conventional surgical cutdown by Torsello (Torsello 2003) in the single randomized study presented. The authors concluded that complications were roughly equivalent in severity. Potential advantages of EVAR without surgical exposure of the femoral arteries are reduced operative time, blood loss, and length of hospital stay which might justify the additional cost for the device (Howell 2002, Traul 2000).

**Fascia suture**

In 1997 Dietrich described a technique by which the cribriform fascia covering the CFA is sutured after percutaneous access (Dietrich 1997) (Figure 1). While surgical cutdown and SMCD involve five to ten minutes of preparation in each groin before application of the Seldinger puncture technique (Seldinger 1953), the fascia suture allows immediate access to the vessel. This is of utmost importance in acute situations such as ruptured aortic aneurysms. In Örebro the first fascia sutures, slightly modified in comparison to the technique described by Dietrich, were performed in 2001. The aim was to develop a technique that could be used as well in elective as in emergency procedures. Since then the fascia suture has been our routine technique in all EVAR and thoracic endovascular aortic repair (TEVAR) procedures and it has also been adopted by other centers (Harrison 2011, Montán 2011, Mathisen 2012).
The Surgiclose technique is yet another mini-invasive method in which access to the target vessel is achieved by exposing only the anterior wall of CFA (Mayer 2008). Single sutures are placed in the horizontal plane, two on either side of the proposed entry point. Via an open Seldinger technique in the midline between the four sutures, sheaths are inserted over the wire. In the end of the procedure all tools are removed and the assistant pulls sutures tight. In the modified “Surgiclose Technique II” only two Z-sutures are placed instead of four single sutures.

Open repair of ruptured abdominal aortic aneurysm
Despite considerable improvements in perioperative care, anaesthesiology and intensive care, operative mortality after RAAA has been reported roughly unchanged at 40-50% (Dardik 1998, Visser 2005) even though a slight decrease has been achieved since the 50th (Bown 2002). In general, a better outcome is reported from hospitals compared to national registers (Blankenstein 1998, Haug 2005). In a meta-analysis including 116 obser-
vational studies comprising over 60,000 patients (1970-2003), the overall mortality rate was 48.5% and did not change significantly over the years (Hoornweg 2008). One explanation is that the mean age of operated patients has increased which may have reduced the effect of improved perioperative care, anaesthesiology and intensive care. In contrast, a considerably lower 30-day mortality rate has been reported from single-centers in Sweden (26%) (Zdanowski 2002) and Switzerland, where octogenarians had a mortality rate of 26.7% and nonoctogenarians 15.3% (Opfermann 2011).

Operative mortality rates increase significantly with advancing age (Dardik 1998) and age is the most important independent risk factor (Visser 2005). Other predictors for outcome after open repair (OR) have been studied. The Hardman index measures five different variables; age, loss of consciousness, haemoglobin, creatinine level and electrocardiographic ischemia. A strong correlation between number of risk factors and mortality has been described (Hardman 1996, Acosta 2006), where age, loss of consciousness and haemoglobin have been confirmed as independent risk factors for mortality (Acosta 2007). Higher annual operation volumes are associated with significantly lower mortality rates in both elective and ruptured AAA repair (Wen 1996, Kantonen 1999, Manheim 1998, Holt 2007).

The surgical technique has not changed much during the last 20 years but postoperative monitoring has been more active. Abdominal compartment syndrome (ACS) is an important complication after OR on patients with RAAA and is associated with colonic ischemia. The incidence is most likely above 10% (Björck 2008). Monitoring intraabdominal pressure with a regular interval and timely intervention may improve outcome (Djavani 2009).

**EVAR of ruptured abdominal aortic aneurysms**

EVAR of a RAAA was first performed successfully by Marin and Veith in 1994 (Marin 1995) and another early case was reported by Yusuf in 1994 (Yusuf 1994). In 2000 Ohki presented the first case series of 25 patients in which 20 patients had been treated by EVAR and with a mortality of just 10 percent (Ohki 2000). Since then many centers have introduced the endovascular technique. In Örebro we performed the first EVAR on a RAAA in 2001. Some groups have developed standardized programs of how to manage RAAA and used EVAR whenever it has been possible and have achieved good results (Lachat 2002, Veith 2002, Resch 2003, Lee 2004, Kapma 2005, Mehta 2006, Coppi 2006, Moore 2007). More modest results have been reported by others, no better than after tradition-
al OR (Peppelenbosch 2006, Hinchliffe 2006). Some centers treat only stable patients but for others hemodynamic instability is not an exclusion criterion. There is also great variability in how instable RAAA patients are resuscitated.

**Logistics**

Although some centers attempt to treat all RAAA with EVAR they are sometimes prevented from doing so as an EVAR trained team (surgeons, radiologists, nurses, radiologic technicians) is not available. Another limiting factor is that stent graft components are not accessible (Reichart 2003). Centers have emphasized the importance of having trained staff available 24 hours a day, 7 days a week. Many have reported improved survival after introduction of an emergency endovascular therapy protocol for RAAA (Mehta 2006, Moore 2007).

In stable patients it is routine to perform a CT angiography or at least a CT without contrast medium in order to confirm the diagnosis, perform the required measurements for EVAR and ultimately decide whether the patient will be treated by endovascular or OR. In unstable patients there are different routines. If an emergent CT is available it will likely be obtained. Some centers routinely avoid CT in unstable patients if the clinical diagnosis is evident and perform a fluoroscopy on the OR. Based on that examination a decision is taken to choose EVAR or OR (Ohki 2000).

**Registries**

Data collected by questionnaires from 49 centers on 1,037 patients treated with EVAR concluded a 30-day mortality of 21.2%. Centers performing EVAR for RAAA whenever possible achieved an EVAR rate of 28-79% (mean 49.1%). The 30-day mortality rate was 19.7% (range: 0%-32%) for 680 EVAR patients, and 36.3% (range: 8%-53%) for 763 patients treated with OR (p<0.0001) (Veith 2009). This survey showed great variation of care between the centers. The majority used modular (82%) instead of unibody (18%) stent grafts. Homemade stent grafts in this series were used in 13% reflecting the early period when industry-made stent grafts still had many limitations.

**Randomized trials**

There is no level one evidence to support that EVAR can be generally justified for RAAA treatment. The encouraging early results of endovascular treatment might have been biased by patient selection (Hinchliffe 2003). The first prospective randomized trial took place between 2002 and 2004. The trial showed no difference between EVAR and OR regarding 30-day
mortality. A major limitation was that only 31% (32/103) of admitted patients could be recruited to the study (Hinchliffe 2006). Another multi-center randomized trial from the Netherlands, the Amsterdam Acute Aneurysm Trial (2004-2008), faced the same problem. Out of 128 patients with confirmed rupture, only 38 (30%) were considered suitable for endovascular treatment (Hoornweg 2007).

In 2009 a European trial was initiated to study whether a preferential strategy of endovascular repair would result in survival benefit (IMPROVE trial 2009). The study is ongoing.

Permissive hypotension
Since long it has been evident that passive or active lowering of blood pressure can improve the outcome of patients with gastro-intestinal bleeding (Andresen 1949, Shaftan 1965). In 2002 Veith suggested that a policy with restricted fluid resuscitation would prove valuable (Veith 2002). Some centers have followed this policy and even used medication to lower the blood pressure, unless there are signs of cerebral or cardiac malperfusion (Yilmaz 2002, Peppelenbosch 2006, van der Vliet 2007, Mayer 2009).

Local anesthesia
To avoid circulatory collapse during the induction of general anesthesia in RAAA patients, the use of local anesthesia supplemented with analgesia with remifentanyl was first reported by Lachat in 2002 (Lachat 2002). Many centers use local anesthesia as the first option and convert to general anesthesia if necessary.

Aortic balloon control
Placement of an intraluminal aortic occlusion in a clinical situation was first described in 1954 by Carl W Hughes, a Lieutenant Colonel active in the Korean conflict, for control of massive intraabdominal bleeding (Hughes 1954). In 1962 Hesse and Kletschka controlled hemorrhage from a RAAA with the same method (Hesse 1962). Open remote aortic balloon occlusion, by a transaxillary approach, to control RAAA was first described in 1977 by Ng and Ochsner (Ng 1977). A Fogarty balloon was inflated in the aneurysm sac and pulled up against the neck as a tamponade. In 1999 Ohki and Veith used a percutaneous technique to insert the occlusion balloon from either a femoral or a brachial artery access (Ohki 1999).

The preferred method is to insert a balloon catheter from the femoral artery and inflate the balloon in a supraceliac position. To prevent from migration a supporting introducer reaching the balloon is also inserted (Ma-
When the main body of the stent graft has been deployed, a second occlusion balloon is inflated inside the stent graft, and the first balloon can be withdrawn. This minimizes visceral ischemia time. The routines vary between different centers. Some use it on all unstable patients and others only in circulatory collapse. A proportion of about 20% use of balloon catheters has been reported (Veith 2009).

**Abdominal compartment syndrome**

ACS is estimated to develop in about 20% of patients after EVAR for RAAA and is a major cause of mortality and morbidity (Mehta 2005). An intra-abdominal pressure >20mmHg in combination with organ dysfunction is defined as ACS but an abdominal pressure above 12mmHg is already considered abnormal (Malbrain 2006). Different techniques to manage the condition have been described as conservative treatment, decompression by open abdomen or with catheter technique. Early conservative treatment with diuretics, colloids, neuromuscular blockade and analgesics to relieve pain has been reported useful in the treatment of ACS (Djavani 2006, Djavani Gidlund 2011).

A laparotomy may be required to decompress the abdominal compartment by evacuation of the hematoma and relieving the high intraabdominal pressure. This procedure also allows for an inspection of the abdominal organs (Mayer 2009, Makar 2009).

Another option to decrease the abdominal pressure is to evacuate blood by insertion of a drain into the hematoma under CT guidance. A t-PA solution is infused to lyse the hematoma for evacuation (Hörer 2012). By combining the catheter drainage with t-PA injection, more effective evacuation of the hematoma can be achieved (Hörer 2011). The major advantage with this mini-invasive technique is that it can performed under local anesthesia avoiding a laparotomy. A disadvantage is that abdominal organs cannot be inspected.

Some centers do not regularly measure intraabdominal pressure, but only in situations when renal and lung function worsen or blood pressure is low (Mehta 2005). Other centers have a more aggressive policy and measure the variables routinely (Mayer 2009).

**Adjunct techniques in EVAR**

**Chimney technique**

The basic principle for the chimney technique is a stent or a stent graft that is deployed parallel to the aortic stent graft into a branch artery. In practice, the chimney is deployed between the aortic wall and the stent graft.
Chimneys were first described in 2003 by Greenberg (Greenberg 2003) as an adjunct technique to treat AAA with short proximal necks. The main stent graft was by intention deployed to partially cover the renal artery ostium and was followed by insertion of a bare stent in the renal artery to secure patency. The same technique was used by our group in 2005 in the aortic arch (Larzon 2005). The proximal landing zone can be extended into the arch by deployment of chimney stent grafts in the subclavian and/or the carotid artery (Figure 2). The procedure is normally combined with debranching of the left subclavian artery, using a bypass graft between the left carotid and subclavian artery.

Figure 2. Chimney stent grafts in the left carotid and left subclavian artery (white arrows) with a thoracic stent graft.

Over time, the chimney technique has been widely accepted as an option for treatment in AAA with short necks or juxtarenal anatomy (Larzon 2008, Ohrlander 2008). Modified branch preserving techniques have also been used in suprarenal aortic aneurysms and thoraco-abdominal aortic aneurysms with up to four branches preserved, but are so far performed
only at highly specialized centers (Kasirajan 2011, Pecoraro 2011, Lobato 2012).

**Embolization techniques**
The presence of a common iliac aneurysm can necessitate extension of the stent graft down to the EIA in order to achieve distal sealing. Specially designed stent grafts have been developed to preserve the internal iliac artery but usually this vessel is occluded to avoid a type II endoleak. The use of mechanical devices, coils or plugs, has been described (Cynamon 2000, Ha 2005) and covering the EIA with a stent graft can also be satisfactory (Papazoglou 2012). Placement of coils or plugs requires a selective and sometimes time consuming catheterisation of the internal iliac artery which has to be achieved before the stent graft is deployed in the EIA. Embolization by injecting a polymer, Onyx (ev3, Irvine, CA, USA), was described by our group and implemented as an adjunct technique in the treatment of RAAA (Larzon 2012).
**Aims of the thesis**

The overall aim of the thesis was to study the outcome of implementation of endovascular techniques in the treatment of abdominal aortic aneurysms.

To study mortality of EVAR and open repair of patients with ruptured abdominal aortic aneurysms  
(Paper I)

To study complication rate for access closure with the fascia suture after percutaneous endovascular aortic repair in a selected patient group  
(Paper II)

To test the hypothesis that access closure time is faster and cost is lower for fascia suture than for a suture-mediated closure device (Prostar) after endovascular repair of patients with aortic aneurysms and dissections  
(Paper III)

To assess whether outcome can be improved for a cohort of patients with ruptured abdominal aortic aneurysms with a preferential EVAR strategy  
(Paper IV)
Patients and methods
The studies conducted in this thesis are clinical studies in patients with non-ruptured or ruptured aortic or iliac aneurysms. Data is retrieved from patient records at Örebro University Hospital (Paper I, II, III and IV) and by prospectively collected study data at Örebro University Hospital and Sahlgrenska University Hospital, Göteborg (Paper III) and from University Hospital, Zurich (Paper IV) (Table 1). Data is also retrieved from the Swedish Vascular Registry.

Table 1  Summary of patients and methods.

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<td>473 patients with ruptured AAA treated at University Hospital of Zurich, 1998-2011, and Örebro University Hospital, 2001-2011</td>
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**Paper I**

A retrospective review was conducted of all fifty patients presented with RAAA at Department of General Surgery, Örebro University Hospital between May 2001 and January 2004. Patient demographics, clinical assessment data, laboratory data and imaging, treatment and outcome (complications and mortality) were gathered. Definitions for a ruptured AAA were verified extravasation of blood on CT and/or free intraperitoneal or retroperitoneal bleeding during laparotomy. Circulatory shock was defined as systolic blood pressure <80 mmHg at any time from arrival at hospital until induction of anesthesia. Five risk factors according to the Hardman score were analyzed (age>76 years, loss of consciousness, hemoglobin <90 g/L, creatinine <190 mmol/L, and electrocardiographic ischemia). Mortality, defined as death within 30 days after operation, or if hospital stay exceeded 30 days, then in–hospital mortality was registered. Postoperative complications were classified as either major or minor complications. Major complications were those leading to death, multi-organ failure, intensive care unit stay >5 days, cerebral complication, limb amputation and conversion to open surgery. Minor complications were other sequelae without any permanent disability.

Twenty-six (52%) patients (23 men; median age 75 years, range 60-84 years) had an OR and 15 (30%) patients (14 men; median age 73 years, range 58-85 years) were treated with EVAR. In the OR group 38% were in circulatory shock and corresponding figure was 73% in the EVAR group. Nine (18%) patients (5 men; median age 86 years, range 77-91 years) were not operated upon.

**Paper II**

A retrospective review of the fascia suture technique (FST) was conducted on a consecutive series of patients undergoing elective or emergency treatment of abdominal and thoracic aortic aneurysms, thoracoabdominal aortic aneurysms, iliac aneurysms, aortic dissections and plaque ruptures. Both primary and secondary interventions were included in the study. Between August 2001 and September 2004, 127 patients (103 men; median age 74 years, range 45-89 years) were treated. Twelve patients had secondary interventions for a total of 139 procedures.

Data was collected for analysis of access site complications after access closure with the fascia suture. Perioperative complications were defined as those occurring at the fascia sutured access site leading to an additional perioperative procedure and postoperative complications were either early (<24 hours after operation) or late (>24 hours).
Ankle-brachial index (ABI) was recorded before and after the procedure and, at follow-up in a subgroup of patients and was compared with ABI in limbs with other closure methods. Emergency patients were not included as preoperative ABI was not registered as a routine.

A subgroup of patients was also investigated by duplex ultrasonography after the procedure. CFA and the proximal superficial femoral artery were examined. A significant stenosis was defined as a maximum systolic flow velocity at least twice that of the preceding vessel segment.

**Paper III**

A prospective, randomized, two-centre trial was performed on patients undergoing EVAR or TEVAR for aneurysm or dissection. Between 2006 and December 2009 one-hundred patients were randomized. Primary endpoints were procedure time for access closure and cost for the FST and Prostar technique. Technical failure was defined as perioperative and immediate postoperative complications. Outcome was recorded peroperatively, postoperatively, at discharge, at 30 days and at 6 months follow-up.

Inclusion criteria were patients planned for EVAR or TEVAR for aneurysm or dissection, planned femoral access and planned for at least 16 F outer diameter of introducer or stent graft system on the main access site. Exclusion criteria were aorto-uni-iliac stent-grafts with femoro-femoral bypass, femoral aneurysms, ruptured aneurysms, emergency operations without preoperative ultrasound and ongoing anticoagulation treatment with warfarin.

In the power estimation of the sample size we calculated for a superior hypothesis with a median access closure time of 13 minutes for FST and 23 minutes for Prostar. The cost for the Prostar was calculated to be 3-4 times higher than for FST. With a significance level of 5% and statistic power of 90%, it was decided to randomize 45 patients in every arm, together 90 patients, stratified on hospital. The sample size was increased to 100 patients because of differences in inclusion rate between the two centers.

**Paper IV**

A retrospective review of 473 consecutive patients with ruptured AAA recruited at University Hospital of Zurich between 1998 and 2011 (295 patients) and Örebro University Hospital between 2001 and 2011 (178 patients). In these patients the intention was to treat with “EVAR-whenever-possible” approach until April 2009 (EVAR/OPEN period), and after that the intention was a “100% EVAR” approach (EVAR-ONLY period).
Rupture was defined as blood or contrast visible outside the aortic wall, detected either by preoperative CT, intraoperative angiography or during surgery. A contained rupture was defined as blood or contrast confined to the retroperitoneal space and a free rupture as blood or contrast visible within the peritoneal cavity (with or without retroperitoneal bleeding). Fistula was defined as aneurysm rupture into any visceral organ (bowel, ureter) or vessel (inferior caval vein, renal vein). Patients with no endovascular or surgical treatment were defined as medically treated.

Exclusion criteria were ruptured thoracoabdominal aortic aneurysms Crawford type I-IV, suprarenal RAAA and ruptured isolated iliac aneurysms. Four patients were rejected due to staff or facility availability and excluded from the analysis. Data from both centers were merged into one single database.
Statistical methods

In the studies of this thesis, categorical variables were summarized with percentages and analyzed using the Chi-square test or the Fisher’s exact test. Mean and standard deviation (SD) was used to summarize continuous variables with symmetric distribution and median (range) was calculated for non-symmetric distributions. Continuous variables with approximately normal distributions were analyzed with the two-sample t-test or the unpaired Student t-test. A p-value <0.05 was considered statistically significant.

In Paper I an exact method for handling small sample sizes was used to estimate logistic regression with mortality as the outcome variable and study group as independent variable, both unadjusted and adjusted for other risk factors. Analyses were performed using Logexact (version 4.10; Cytel Software Corp., Cambridge, MA, USA).

In Paper II data were presented as median (range) or percentage. Generalized linear model for repeated observations with unstructured covariance structure was used to analyze the association between outcome variable complication and sheath outer diameter. Measure of association is odds ratio with 95% confidence intervals. Analyzes were performed using the Stata statistical software (release 9; StataCorp LP, College Station, TX, USA).

In Paper III a linear regression was performed to analyze outcome variable (procedure time) after logarithmic transformation due to skewed distribution. Both unadjusted and adjusted models were fitted using SPSS version 17 (Chicago, IL, USA). For cost analysis, 95% confidence intervals for median differences of total cost between study groups were estimated by Hodges-Lehmann method using STATA release 11 (College Station, TX, USA).

In Paper IV logistic regression was used to compare outcome between two groups. Both unadjusted and adjusted models for other potential markers were fitted. The adjusted model was further evaluated by pairwise interaction test between groups and the other markers in the model, one by one. If the interaction test was statistically significant at p<0.20 they were reported in the text, otherwise a two-tailed p-value <0.05 was considered statistically significant. SPSS Version 17 (Chicago, IL, U.S.A) was used for statistical analyses.
Ethics

The randomized trial (Paper III) was approved by the Regional Ethical Review Board in Uppsala and patient informed consent was obtained by all patients. The retrospective analysis (Paper IV) was approved by the Local Ethical Board in Zurich, Switzerland and for the cohort from Sweden, the Regional Ethical Review Board in Uppsala gave the approval. All patients, still alive, were sent a letter and all gave informed consent. Two patients were not able to reach.
Specific methods

Fascia suture technique (Paper I, II, III and III)

After completion angiography has been performed the introducer with its dilator is left in place over a stiff guidewire. A dissection down to but not through the cribriform fascia is performed. One stitch in the fascia on each side of the introducer in the longitudinal direction of, but not including, the artery is performed using a monofilament suture followed by withdrawal of the introducer (Figure 3). If a bleeding problem exists the operator can reinsert the introducer to allow supplementary suturing.

Figure 3. (A) Stitches in the fascia on each side of the introducer. (B) The slip-knot is tightened as the introducer is withdrawn. (drawings produced by Peter Grahn)


Double balloon technique (Paper I and IV)

An aortic occlusion balloon is applied only when the patient is hemodynamically unstable. We insert a balloon catheter from the femoral artery and inflate the balloon in a supraceliac position. To prevent from migration a supporting introducer reaching the balloon is also inserted. When the main body of the stent graft has been deployed, a second occlusion balloon is inflated inside the stent graft (Figure 4) and the first balloon can be withdrawn.
Figure 4. Two occlusion balloons are inflated and supported by introducers. The distal balloon is inflated in the body of the stent graft.


**Chimney technique (Paper IV)**

Chimney grafts have been used in patients with an insufficient proximal aortic neck in order to deploy the fabric-covered part of the stent graft proximal of the renal arteries. Chimney stent grafts are inserted from above, either through a percutaneous brachial access in the elbow or through an open access of the axillary artery. Guidewire and introducer access to one or both of the renal arteries is established and then the chimney stent graft is delivered through the introducer to the target vessel. The main stent graft is inserted and deployed. Immediately thereafter the chimney(s) are deployed (Figure 5).
Onyx embolization technique (Paper IV)

Patients having aorto-iliac engagement of the aneurysm are treated with embolization of the common and internal iliac artery to prevent back bleeding into the aneurysm. A separate catheter is left in the common iliac aneurysm outside the deployed stent graft and Onyx is injected to fill the aneurysm and the proximal part of the internal iliac artery (Figure 6). The technique does not require direct catheterization of the internal iliac artery.
Lytic-assisted catheter decompression (Paper IV)

Some of the patients have decompression with a lytic-assisted catheter decompression technique. A CT is performed to identify the hematoma and a puncture site on the skin is decided. Under local anesthesia a 20 F catheter is inserted to the hematoma and spontaneous blood coming through the drainage is collected (Figure 7). When there is no longer any spontaneous blood flow from the drainage, a solution of 20 mg t-PA (Atlepas, Boehringer Ingelheim, Germany), dissolved in 200 ml natrium-chloride is injected into the drainage. The catheter is clamped for 20 minutes and then additional blood can be collected.
Figure 7. (A) Post EVAR CT imaging showing the hematoma location and size. (B) Drain insertion with sequenced use of dilators. (C) CT-guided puncture with a 20 F catheter directed into the center of the hematoma. (D) The catheter is connected to a urinary bag.

Results

Paper I
The mortality rate after EVAR was 13% (2 of 15) compared to 46% (12 of 26) in the OR group (univariate odds ratio = 5.4, 95% CI, 0.9-58, p=0.067; and multivariate odds ratio = 6.5, 95% CI, 0.8-96, p=0.079). Multivariate analysis of mortality in relation to circulatory shock and the selected 5 risk factors did not produce any statistically significant differences between the groups. The only significant difference was recorded for the cohort with the greater number of 2-4 risk factors where the mortality was higher (odds ratio = 5.5, 95% CI, 1.0-42.0, p=0.048). There was no significant difference in the rate of total complications between the groups, however, significantly more major complications were recorded in the OR group (p=0.049). Selection to either EVAR or OR was significantly related to whether the vascular surgeon had endovascular experience or not.

Paper II
FST was used for closure in 52% (131/250) of CFA accesses. For the largest introducer or stent graft sizes with an outer diameter of 20-27 F, FST was used in 79% (100/127). The study showed an acute failure rate of 12.2%. Half of failures appeared perioperatively and the rest postoperatively, requiring reoperations within 24 hours. During follow up, two patients (1.5%) had late complications. One of them had a pseudoaneurysm that was treated surgically and the other had a neuralgia. There was a trend for more complications when larger introducers had been used (odds ratio = 3.2, 95% CI, 0.6-15.3, p=0.153). Complications were equally distributed throughout the study period.

ABI values did not change significantly from pre- to postoperatively for either the fascia suturing (p=0.93) or other closure methods (p=0.94). Fifty patients with 66 fascia sutures underwent ultrasonography at a median of 4.5 months (range 4–27) postoperatively. Five significant stenoses were detected but none of these patients had clinical symptoms or a significant drop (>0.10) of ABI or required any intervention. Three pseudoaneurysms were also detected but did not require treatment.

Paper III
The randomized trial showed a significantly shorter access closure time with FST (median 12.4 minutes) than with Prostar (median 19.9 minutes). The latter required a 54% longer procedure time (group difference 1.54, 95% CI, 1.25-1.90, p<0.001). An independent risk factor was operator
experience where the difference was 1.30 (95% CI, 1.09-1.55, p=0.005). Operators were required to have an experience of minimum 15 FST and 15 Prostar procedures to reach the basic competence level. The proficiency level for a technique was set to 60 procedures. Stratified on operator experience, the group difference for operators at proficiency level was 1.25 (95% CI 1.05-1.49, p=0.014) and for operators at basic level 1.33 (95% CI, 1.01-1.75, p=0.044).

There was a significant difference of cost in favor of FST with a median difference of 800€ (95% CI, 710-927, p<0.001). In the Prostar group, 50% of the total cost was caused by material.

The technical failure rate was 15% (7/48) for FST and 24% (12/51) for Prostar (p=0.259). The proficiency level group had a technical failure rate of 4% (1/26) for FST and 7% (1/14) for Prostar, while corresponding rate were 27% (6/22) for FST and 30% (11/37) for Prostar for the basic level group.

Late complications were recorded in 4% (2 patients) for FST and 10% (5 patients) for Prostar. One of the patients in the FST group had a pseudoaneurysm and also 4 patients in the Prostar group. None of them required reintervention. Preoperative, postoperative, 1 and 6 month follow-up ABI measurements were completed by 89 patients (90%) and values did not change significantly for any group.

**Paper IV**

30-day mortality for the total cohort (including the 42 medically treated patients) was 31.9% (151 of 473). Overall combined (EVAR and OR during the whole study period) 30-day mortality was 25.3% (109 of 431). For the EVAR group mortality was 17.9% (48 of 268) and for the OR group it was 37.4% (61 of 163) during the entire study period (absolute risk reduction = -0.195, 95% CI, -0.282 to -0.108; relative risk = 0.48, 95% CI, 0.35-0.66; relative risk reduction = 52%, 95% CI, 34% - 65%)

The total cohort mortality (including medically treated patients) for the EVAR/OPEN period was 32.8% (131 of 400), compared with 27.4% (20 of 73) for the EVAR-ONLY period (p=0.367). During the EVAR/OPEN period, 10% (39 of 400) of patients were treated medically compared with 4% (3 of 73) of patients during the EVAR-ONLY period. Thirty-day mortality for EVAR gradually increased from 10.8% (1998-2004) to 18.5% (2005-2009) and to 24.3% during the EVAR-ONLY period (2009-2011).

Adjunctive EVAR procedures during EVAR-ONLY were used in 24% compared to 9% patients during EVAR/OPEN period.

During the time period from 1998 to April 2009, OR showed a statistically significant association with 30-day mortality compared with EVAR
(unadjusted odds ratio = 3.2, 95% CI, 1.9-5.3, p<0.001). When adjusting for other potential markers for 30-day mortality (age, sex, type of rupture, hemodynamics, anesthesia, abdominal decompressing, center, time period) no major change was found (adjusted odds ratio = 3.3, 95% CI, 1.4-7.5, p=0.004). Independent markers for mortality were age >75 years and free rupture while hemodynamic instability, general anesthesia and the need for laparotomy were other markers, although not independent.

During the same period it was investigated if the two groups (EVAR and OR) interacted with other markers for mortality. One interaction test was statistically significant. EVAR and OR were not independent of abdominal decompression. For patients with no abdominal decompression, there was a large decrease in 30-day mortality for EVAR compared with OR in favor of EVAR (unadjusted odds ratio = 5.1, 95% CI, 2.7-9.6; and adjusted odds ratio = 5.6, 95% CI, 1.9-16.7). On the contrary, in patients in whom abdominal decompression with laparotomy was performed no decrease in mortality was observed for EVAR compared with OR (unadjusted odds ratio = 1.1, 95% CI, 0.4-3.2; and adjusted odds ratio 1.1, 95% CI, 0.3-3.7). A trend of increased 30-day mortality was seen for the EVAR group in the second period (2005 to 2009) compared with the first period (1998 to 2004), (unadjusted odds ratio = 1.9, 95% CI, 0.8-4.5; and adjusted odds ratio = 1.7, 95% CI, 0.6-4.6) whereas for OR there was a minor trend toward decreased mortality between the same periods (unadjusted odds ratio = 0.7, 95% CI, 0.3-1.4; and adjusted OR = 0.6, 95% CI, 0.2-1.5).
Discussion

The first study includes data from the very early period of EVAR in the treatment of RAAA. A critical question was how to implement EVAR in an open surgery environment. The typical scenario for an unstable patient with symptoms predictive for a ruptured aneurysm was an immediate transport to the operating theater for careful induction of general anesthesia and laparotomy. Under favorable conditions, proximal aortic clamping could be achieved within five minutes. CT was never performed in patients presenting as described.

In our first study it was mandatory to perform a preoperative CT for doing an EVAR, which could only be achieved in 73% (30 of 41 patients) of the patients having an operative treatment. Six of the patients in whom CT was not performed were in circulatory shock and for the other five patients, who were circulatory stable, a decision to make an OR was taken already in the emergency room and the patient was transported directly to the operating theater. Among the 41 treated patients, four were excluded from EVAR because of anatomical limitations. Two patients had a too short proximal aortic neck and one patient had narrow access vessels. The fourth patient had a CT without contrast and it was not possible to properly evaluate the morphology of the proximal neck.

Sometimes OR was considered as the best option for the patient based on the competence of the vascular surgeon on call or unavailability of sufficiently trained endovascular personnel, thus bias selection was inevitable. Registration of proper baseline data was important. Systolic blood pressure was recorded as a marker for hemodynamic instability, with a cut-off value of <80 mmHg. There is no evidence for what is circulatory instability. Some centers use a lower cut-off and some quantify between hypotension <70 mmHg and circulatory collapse <50 mmHg (Veith 2009). Another definition is to calculate shock index from the quotient of heart beats/minute and mmHg.

We also used the Hardman score, evaluated in OR where number of risk factors (maximum 5) where associated with outcome (Hardman 1996). Our results supported previous observations as mortality was significantly higher for patients with 2-4 risk factors than for those with 0-1 risk factors. The Hardman index has also been reported in other studies as a useful predictive tool after EVAR correlating with mortality rate increasing along with the Hardman index (Acosta 2006, Conroy 2011), but cannot be used to accurately identify patients with no chance of survival after endovascular repair (Karkos 2008). The Glasgow aneurysm score (GAS) is another preoperative risk scoring scale and it has been validated together
with the Hardman index in patients operated for RAAA. It has been found that these two scoring scales have a significant correlation with in-hospital mortality rate (Kurc 2012).

Our study showed a trend for lower EVAR mortality than after OR (13% versus 46%, p=0.067) in line with other studies during that period; Alsac 23.5% versus 50%, p=0.09 (Alsac 2005), Greco 39.3% versus 47.7%, p=0.05 (Greco 2006), Kapma 13% versus 30%, p=0.02 (Kapma 2005).

All studies, including our own were subject to patient selection and could not support use of EVAR on high quality evidence. In a Cochrane review from 2007 it was stated that EVAR was feasible in selected patients, with outcomes comparable to best conventional open surgical repair for the treatment of RAAA. Furthermore, endovascular repair in selected patients might be associated with a trend towards reduction in blood loss, duration of intensive care treatment, and mortality (Dillon 2007).

Based on the results in our first study, a program was initiated to expand the use of EVAR in the treatment of RAAA. The first goal was to improve logistics. As a first step it was mandatory to consider endovascular treatment in all patients, which required endovascular staff continuously available.

The next goal was to implement a new strategy. Unstable patients had previously been treated liberally with occlusion balloons increasing the risk for splanchnic and lower body ischemia and reperfusion injury. In 2000 Ohki and Veith described the use of hypotensive hemostasis by minimizing fluid resuscitation and allowing the blood pressure to fall as low as 50 mmHg provided the patient was not unconscious or had signs of myocardial ischemia (Ohki 2000). In our first study we had used occlusion balloons in 73% (11/15) of the patients. After adapting the concept of permissive hypotension, the use of occlusion balloons was reduced to 32% (38/118) of the EVAR procedures. We also increased the use of local anesthesia according to the Zurich group (Lachat 2002).

The last goal was to implement new catheter-based techniques. In order to treat AAA with extension down to the iliac arteries we started to use Onyx in 2005 to embolize the internal iliac artery to prevent back bleeding into the aneurysm and 1 year later chimney grafts were introduced to treat short necks or juxtarenal aneurysms. By using these adjunct techniques both centers (Örebro and Zurich) were able to almost replace OR with EVAR by May 2009. Thereafter, an EVAR/ONLY period started, compared to the previous period (EVAR/OPEN).

The most remarkable effect was that patients allocated to “Medical treatment” (no operations) decreased during EVAR/ONLY to 4% (3 of 73)
compared to 10% (39 of 400) during EVAR/OPEN, while the surgical mortality was kept at an unchanged level, 24.3% versus 25.5% during EVAR/OPEN.

The non-operated group is rarely reported in studies why its effect on the entire cohort mortality cannot be compared. In a national-based study from United States outcome after EVAR and OR was studied for patients undergoing operative treatment for RAAA during 2001-2006. EVAR had lower overall in-hospital mortality than OR (31.7% versus 40.7%, P < .0001) but only 11.5% were treated with EVAR and patients who did not undergo either open or endovascular repair were excluded (McPhee 2009). In a meta-analysis of a population-based and hospital-based subgroup of 42,221 respectively 667 patients EVAR was associated with lower mortality than OR (odds ratio = 0.49; 95% CI; 0.35-0.69), but the medical treatment group had not been interpreted (Takagi 2011).

A major limitation of the published meta-analyses is the selection bias why firm conclusions about outcome for the two treatments cannot be drawn. A randomized trial could solve this problem provided that the vast majority of the cohort could be randomized. This has not been the case (Hinchliffe 2006, Hoornweg 2007). Another limitation is that the decision to just treat patients medically differs greatly between centers, which will have a significant effect on the mortality rate. Age is an independent risk factor for mortality and age limits for treatment also varies between centers. Patients advised to medical therapy are usually older, which was seen in our first study (median age 86 years, range 77–91 years) compared to median age 75 years, range 60–84 years for patients operated on. Nine of 50 patients (18%) were offered medical treatment in contrast to 4% during the EVAR-ONLY period. This probably resulted from the fact that some patients who would have required open repair for anatomical reasons were deemed unfit to be subjected to it, whereas they could often be treated successfully by EVAR during the EVAR-ONLY period. Anatomic selection and hemodynamic stability biases to explain improved EVAR results, should therefore be ruled out as confounding factors explaining our mortality rate.

P-EVAR has gained great interest as it may reduce surgery time and decrease time to ambulation and it has been widely accepted. Technical success rate with SMCD closure devices has been reported to 89-95% and late complications around 2% (Malkawi 2010) and this is in line with results of FST from our first study and what has later been reported (Harrison 2011, Montán 2011, Mathiesen 2012). A disadvantage with SMCD is that
pre-suturing is necessary why SMCD has not been attractive in circulatory instable patients. We found that FST was applicable even in RAAA.

Patient selection has been advised for the use of SMCD. The presence of calcification, significant arterial tortuosity or scarring from previous punctures or surgery tends to deflect the device’s needles upon deployment causing closure failure. Additionally, obese patients have a high incidence of failed hemostasis due to the technical difficulty in advancing the device’s slipknots through the extended subcutaneous access canal. Cases involving any of these conditions had a higher frequency of femoral artery cut down conversion and device failures (Teh 2001). Calcification of FCA has been the most common exclusion criterion in reported studies (Jean-Baptiste 2008, Dosluoglu 2007, Watelet 2006, Borner 2004, Howell 2001, Teh 2001, Traul 2000) together with scarred groins (McDonnell 2008, Jean-Baptiste 2008, Watelet 2006, Howell 2001, Teh 2001) and femoral aneu-rysrm (Starnes 2006, Torsello 2003, Teh 2001). In our study 57% of the cases were selected for FST but for the largest introducers/stent grafts FST was used in 79%. In 5% a femoro-femoral bypass was performed and in the remaining 16% another method was chosen by the surgeon.

ABI data and ultrasonography findings at follow-up gave support for FST not causing significant femoral stenosis. Pseudoaneurysms were revealed in 4.5%, but only one patient (0.8%) required a reoperation. The incidence of pseudoaneurysms after catheterization ranges from 0.6% to 6% according to the literature (Fellmeth 1991, Chatterjee 1996) with around 1% reintervention rate after percutaneous EVAR (Starnes 2006, Lee 2008, Perdikides 2012).

We found a trend for more complications in patients where larger introducers had been used, a finding that has also been reported for SMCD. In a meta-analysis of 1440 patients and 2447 femoral access sites when percutaneous EVAR were performed, pooled data revealed that the success rate was significantly higher for sheaths ≤18 F (Georgiadis 2011).

A limitation of the feasibility study was the potential bias in the selection of closure method by the surgeon and it was a logical next step to design a randomized trial. The hypothesis of the randomized trial was based on our results from the feasibility study and the experiences of the Prostar device from the group in Göteborg. At that time no randomized trial had been performed between FST and SMCD and so far our trial still is the only one. Torsello performed a randomized trial between Prostar and open surgical access and found a roughly equivalent complication rate (Torsello 2003).

The two participating centers had different protocols, in one FST was the routine technique and in the other Prostar. The two techniques were
applied and harmonized with a strict protocol for both centers. In early studies with the Prostar device a relatively high complication rate (15%-25%) was reported (Traul 2000, Teh 2001). Fifteen procedures were recognized as a minimum request and 60 procedures were used as an arbitrary measure of proficiency. We found that experience level was an independent risk factor and a lesson learned from this trial is the importance to get a proper training program implemented. Our data showed a significant difference in complication rate between experienced operators and those on basic level. Our arbitrary cut-off of, fifteen procedures, was either to short or suffered from not being supervised enough. Today the device company recommends supervised deployment in 10 patients prior to independent use. We have also found that the puncture technique is important. Too high or too low puncture should be avoided as well as lateral or medial puncture of the arterial wall.

There is evidence for reduced procedural time, time to discharge and time to ambulation when using a percutaneous technique and Prostar instead of surgical cut-down (Haulon 2011). Our trial showed that with the use of FST, access closure time is significantly shorter than with Prostar. We found a median time difference of eight minutes which in the context of a procedure time in the range of 2 hours might look marginal. Our study design, requiring a preoperative ultrasound, demanded exclusion of RAAA. That indication is probably the most interesting. With shorter access closure time and the advantage of not to apply pre-suturing, FST is probably of more benefit in emergency situations than in elective operations and both centers have also implemented FST as the standard method in the treatment of RAAA (Paper I and IV).

Health economic arguments have become gradually more important in clinical decisions, especially when new types of treatments are introduced. Cost analysis is however complex especially when it comes to a comparison of two quite different modalities as EVAR and OR. In an analysis of data from publications between 2003 and 2008, Mani found a skewed distribution of cost data and the estimated total cost of elective AAA repair including 2.5 years of follow-up was similar for EVAR and OR, with a mean cost of €28,193 (Mani 2010) and regardless of medical fitness cost are similar (Jonk 2007). In our study the median cost difference was €800, a minor but not negligible cost saving.

If EVAR is going to be a widely accepted method and replace OR as a standard technique it has to be proven on a high evidence level that outcome is better both for elective and emergency repair or it has to be proven that EVAR is at least more cost effective compared to OR. From this
thesis it can be concluded that knowledge and technology exist today to replace OR and that cost can be reduced.
Conclusion

- There is a trend for lower mortality after EVAR than after open repair in patients with ruptured abdominal aortic aneurysms (Paper I)

- Access closure with the fascia suture after percutaneous endovascular aortic repair has an acute complication rate of 12% in a selected patient group (Paper II)

- Access closure with the fascia suture after endovascular repair of aortic aneurysms and dissections is significantly faster and cheaper compared to the suture mediated closure device, Prostar (Paper III)

- It is possible to replace open repair with EVAR and keeping a low 30-day mortality rate and few patients advised to medical treatment only (Paper IV)
Future aspects

Endovascular treatment has gradually increased at the expense of OR. The open surgery technique has been stationary for a long period and new frontiers as laparoscopic aortic surgery has not convinced the society and future direction will for sure be in the endovascular area. This mini-invasive approach will be driven by patient demand, by attraction from the new generation of physicians and by the willingness of the industry to invest. One can expect that a galloping technological progress in the near future will give the proper tools for treating the pathologies in the aortic arch, the ascending aorta and the heart valves.

Routine endovascular treatment will probably be even easier to perform and new treatment modalities will find their place. Polymer treatment of aneurysms is already an alternative and flow modulators might work at least in selected cases.

Research will surely be focused on prevention, biomarkers and medical treatment to slow aneurysm growth but in a global perspective optimal treatment of RAAA will have high priority.

It is hard to believe that anything but EVAR will be the “golden” treatment for ruptured aortic aneurysms. Randomized trials will be of limited value as long as the inclusion rate is low. Results will be difficult to generalize.

The fascia suture has proven to be competitive with suture devices but has until now not attracted a wider group. This may change, provided that it will be practically possible to implement training programs.

It was a bit surprising that the fascia suture worked that well. But how can it come that it is possible to leave an up to 9 mm big hole in an artery and just use biologic tissue for sealing and the artery “heals” and no stenosis develops? What is the inflammatory response and how does the healing occur? That might be the most exciting spin-off of my thesis.
Summary in Swedish
Sammanfattning på svenska

Trots betydande förbättringar av det operativa omhändertagandet, anestesi och intensivvård rapporteras dödligheten efter öppen kirurgi av brustet bukaortaaneurysm så hög som 40-50% med bara en lätt nedgång sedan 50-talet. Endovaskulär operation av brustet bukaortaaneurysm utfördes för första gången framgångsrikt 1994 och den första patientserien är 2000 redovisade bara 10 % dödlighet.

I avhandlingens första studie gjorde vi en retrospektiv genomgång av endovaskulär operation och öppen kirurgi på 41 patienter med brustet bukaortaaneurysm och fann en trend för lägre dödlighet efter endovaskulär operation (13 %) jämfört med 46 % i den öppet opererade gruppen.

I den andra studien analyserade vi retrospektivt komplikations frekvens av kärlöverläggning med fascia sutur av 131 kärl. Tolv procent av förlustningarna fick komplikationer varav hälften upptäcktes och åtgärdades under operationen och resterande upptäcktes och åtgärdades inom 24 timmar efter operationens avslutning. Ankeltrycket mättes före och efter operationen och var oförändrat.

I den tredje studien utförde vi en prospektiv randomiserad studie vid två centra på 100 patienter som behandlades med endovaskulär operation för aortaaneurysm eller dissektion där kärlöverläggning med fascia sutur jämfördes med ett mekaniskt förlutningssystem (Prostar). Vi fann att förlutningstiden var kortare och kostnaden lägre för fascia sutur än för Prostar. Den senare krävde 54 % längre förlutningstid och medianskillnaden i kostnad var 800€. Komplikationsfrekvensen var inte signifikant skild. En oberoende riskfaktor var operatörens erfarenhet.

Den fjärde studien var en retrospektiv genomgång av 473 patienter med brustet bukaortaaneurysm som rekryterades 1998-2011 vid två centra för att utvärdera hur en förstahands strategi att operera endovaskulärt skulle påverka utfallet. Studien visade att det var möjligt att ersätta öppen kirurgi med endovaskulär operation och att hålla en låg dödlighet (24 %) med få patienter (4 %) som enbart erbjuds palliativ behandling.

Ur den här avhandlingen kan man konkludera att teknologin existerar idag för att ersätta öppen kirurgi med endovaskulär operation och att kostnaden kan minska.
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